SYNTHESIS, STRUCTURAL, AND BIOLOGICAL ACTIVITY OF OLIGOMERS DERIVED FROM *MUCO*-INOSITOL AND CONDURITOL-F

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2003

Dedicated to Nekisha

ACKNOWLEDGMENTS

I would like to thank my research advisor, Dr. Tomas Hudlicky, for his guidance during my tenure at the University of Florida. I truly appreciate the support he has given me. He has been instrumental in my professional development.

My gratitude also goes to Dr. William Dolbier and Dr. Dennis Wright for their support. Also I would like to thank the other members of my committee, Dr. Vanceia Young and Dr. Kenneth Sloan, for providing their support and guidance.

I would also like to thank the rest of the faculty in the Chemistry Department, especially Dr. James Deyrup and Lori Clark, for making my transition back to the University of Florida as smooth as possible.

Special thanks go to the members of Dr. Hudlicky's research group. Their support and friendship have meant a lot. I would especially like to thank Vu Bui and Mary Ann Endoma for the production of *cis*-diol. Without their help this research would not have been possible.

Very special thanks go to Dr. Kofi Oppong and Dr. Jerremey Willis. Our friendship has enriched my life and made this difficult time bearable.

I would like to thank Merck Research Laboratories for allowing me the opportunity to obtain my doctoral degree. Also my gratitude goes to the Florida Educational Fund for their support through the McKnight Doctoral Fellowship. Their support meant volumes.

Finally, I would like to thank my wife, Nekisha Freeman. Her support and understanding through these trying times are very much appreciated. Without her love, this would not have been possible.

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Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
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SYNTHESIS, STRUCTURAL, AND BIOLOGICAL ACTIVITY OF OLIGOMERS DERIVED FROM MUCO-INOSITOL AND CONDURITOL F

By

Stanley L. Freeman

May 2003

Chair: Tomas Hudlicky
Major Department: Chemistry

A chemo enzymatic synthesis of novel inositol oligomers is reported. The starting material used for the preparation of all oligomers was obtained by whole-cell fermentation of bromobenzene with *E. coli* JM109 (pDTG601). Using an iterative methodology, the key sequence was the coupling of homochiral vinyloxiranes in a regio- and stereocontrolled fashion to furnish inositol and conduritol oligomers. With this strategy, repetition of the initial coupling to build higher order oligomers were prepared. A significant step presented in this synthetic route consisted of a selective electrochemical reduction of a vinyl bromide in the presence of cinnamyl ether. All compounds were fully characterized and evaluated for their inhibitory properties against six commercially available glycosidase.

CHAPTER 1
INTRODUCTION

Oligosaccharides have received much attention because of their biological properties and therapeutic potential. Natural oligosaccharides play a pivotal role in molecular recognition, catalysis, signal transduction, and transport processes. Synthetic compounds that mimic the natural oligosaccharides can modulate cellular process and have pharmaceutical benefits.

Recently, the synthetic community has focused on unnatural oligosaccharide derivatives where the endocyclic oxygen atom has been replaced by a methylene unit. These unnatural derivatives have been found to be inhibitors or modulators of important metabolic functions, such as insulin release and specific types of enzyme inhibition.

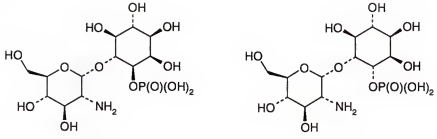


Figure 1. The structures of some putative insulin mimics

Since it was discovered in 1996 that insulin mimetic phospholigosaccharides are present in rat hepatocytes,[1] considerable interest in the synthetic community has been devoted to this area as well as to the preparation of glycosyl phosphatidyl

inositol anchors.[2, 3] Furthermore, it has been suggested that glycopyranosyl cyclitols can act as putative insulin mimics, and especially phosphorylated inosityl glycans have been found to act as a substitute for insulin *in vitro*.[4] Figure 1 shows the structures of some of these putative insulin mimics.[5-8] The latter compound has also been shown to display modest insulin agonist activity

This thesis gives an extensive review of inositol and conduritol syntheses. A review of cyclitols and cyclitol oligomers will also be presented in detail. In the discussion section, the synthesis of *muco*-inositol and conduritol oligomers will be presented along with their inhibitory activity against glycosidases. Finally, three-dimensional molecular modeling of the oligomers will be evaluated.

CHAPTER 2
HISTORICAL

2.1 Conduritols

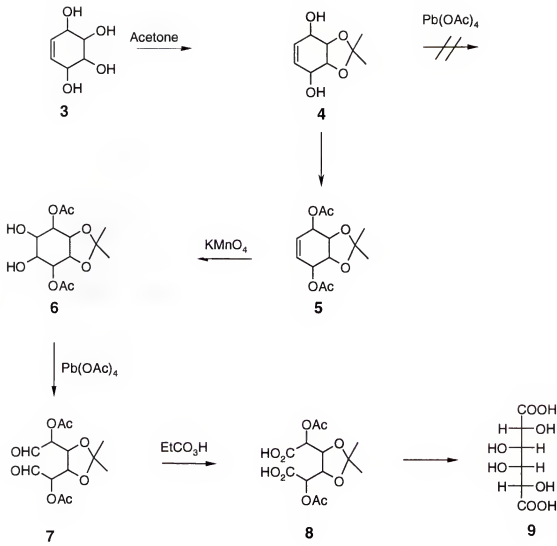
2.1.1 Introduction

In 1908 Kubler isolated the first conduritol from the bark of the vine *Marsdenia condurango*.[9]

3

Figure 2.

Kubler determined that this conduritol was optically inactive and seemingly of unsaturated cyclic constitution. The configuration was established thirty years later by Dangschat and Fischer.[10,11] Conduritol **3** was treated with acetone to yield a mono-acetonide **4**. When treated with $Pb(OAc)_4$, there was no indication of bond cleavage between C_2 and C_3. This supported the fact that C_2 and C_3 were the location of the acetonide. The diacetate **5** was oxidized by $KMnO_4$ to the diol **6**. Treatment with $Pb(OAc)_2$ gave dialdehyde **7**. Further oxidation with $EtCO_3H$ and saponification yielded mucic acid **9** (Scheme 1).



Scheme 1. Dangschat and Fischer's verification of Conduritol-A

Based on these observations, the configuration of Kubler's conduritol was established to be that of conduritol-A. Kern and Frickle later improved the extraction of conduritol-A using chloroform and acetone.[12]

The six possible isomers of conduritol were labeled as A - F to avoid ambiguity.[13] Their structures are depicted in Figure 3.

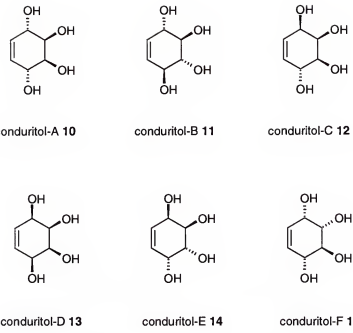
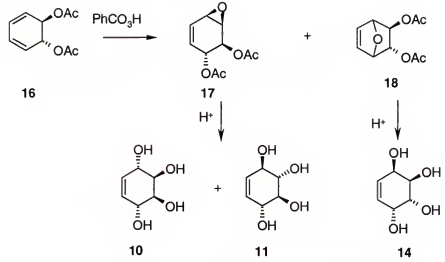


Figure 3. The structures of the six conduritols

Syntheses of the diastereoisomers of conduritols and inositols have been achieved and will be discussed in the next section, where the history, isolation, and derivatives of conduritol and inositol isomers will be presented.

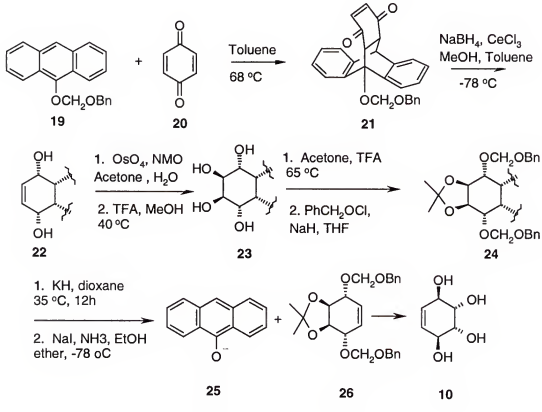
2.1.2 Conduritol-A

Conduritol A and F are the only naturally occurring conduritols. The first successful and non-stereospecific synthesis of conduritol-A **10** was carried out by Nakajima and Tomida in 1957.[14] This synthetic strategy involved the use of benzenediols (Scheme 2). Their synthesis began with the oxidation of diacetate **16** with peroxybenzoic acid to afford the mixture of **17** and **18.** The mixture, without separation, was hydrolyzed with 2N H_2SO_4 to give the three isomeric conduritols -A **10**, -B **11**, and -E **14** which were separated by crystallization and column chromatography.



Scheme 2. The preparation of conduritols by Nakajima

The first stereospecific synthesis of conduritol-A **10** was achieved by Knapp and coworkers in 1983.[15]

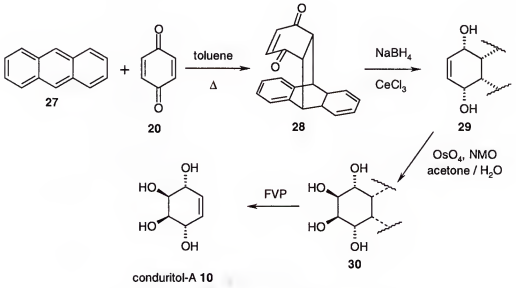


Scheme 3. Knapp's synthesis of conduritol-A

These researchers used *p*-benzoquinone as starting material. One double bond of benzoquinone **20** was protected with 9-[(benzyloxy)methoxy] anthracene **19**. This protecting group blocked one face of *p*-benzoquinone **21** in order to direct *cis*-reduction at C_3 and C_6 and *cis*-functionalization of the remaining carbon-carbon double bond yielding conduritol-A **10** in 39% overall yield (Scheme 3).

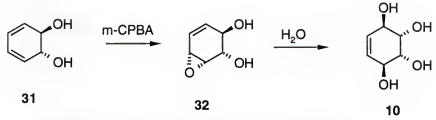
Six years later, Rutledge and coworkers proposed an improved synthesis based on Knapp's work. Rutledge modified the synthesis of conduritol-A **10** which regenerated the olefin by thermal retro Diels-Alder reaction.[16] Rutledge avoided the protection-deprotection sequence required by the oxyanion-accelerated process and improved the overall yield to 72%(Scheme 4).

Diels-Alder adduct **28**, obtained in 86% yield, was reduced under Luche conditions to give diol **29** in 97% yield. Diol **29** was dihydroxylated to furnish tetrol **30** in 87% yield. Flash vacuum pyrolysis (FVP) gave conduritol-A **10** in quantitative yield.



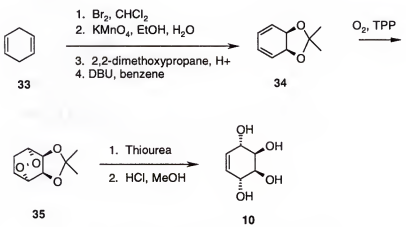
Scheme 4. The Synthesis of conduritol-A by Rutledge.

In 1985, Berchold and Alwksjezh performed a new synthesis of conduritol-A **10** using *trans*-cyclohexadienediol **31** (Scheme 5).[17] With *m*-CPBA, diol **31** was transformed into epoxide **32**. Epoxide **32** was then hydrolyzed with water to afford conduritol-A **10.**



Scheme 5. Berchtold's synthesis of conduritol-A.

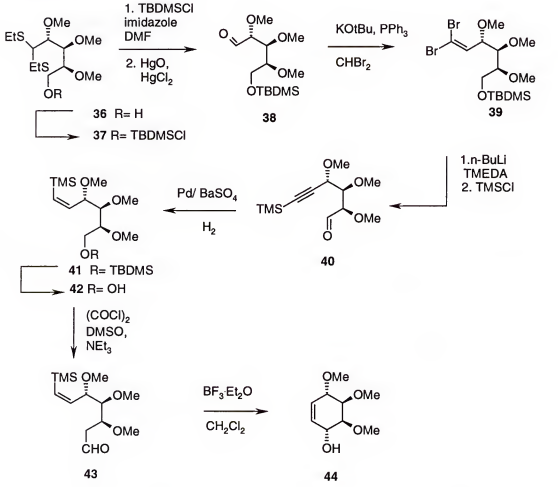
In 1988, the Balci group developed a new stereospecific synthesis of conduritol-A **10** (Scheme 6).[18] The synthesis began with cyclohexa-1,4-diene **33**. Oxidation of **33** followed by protection afforded acetonide **34**. Two oxygen functionalities at the C1 and C4 positions were introduced to **34** by photo-oxygenation. Ring opening of **34** followed by deprotection afforded conduritol-A **10**.



Scheme 6. Balci's synthesis of conduritol-A

In 1989, Carless and Oak also prepared conduritol-A **10** as a side product during their approach toward conduritol-D **13**.[19]

In 1991, the Weinreb group reported a strategy for the synthesis of conduritols via stereodivergent vinylsilane-aldehyde cyclizations to obtain a trimethylated derivative of conduritol-A.[20]

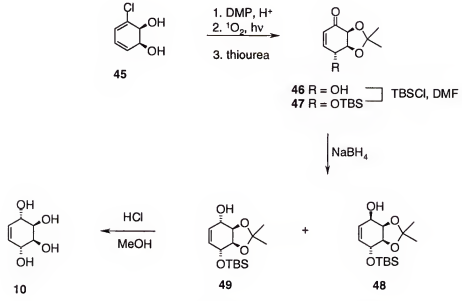


Scheme 7. Weinreb's synthesis of conduritol-A derivative.

Known dithioacetal trimethyl ether[21] **36**, prepared in three steps from l-arabinose, was protected as a silyl ether **37**, and the dithioacetal subsequently removed to yield aldehyde **38**. Wittig olefination of **38** afforded the dibromide **39**, which was converted to the silylacetylene **40** using Corey-Fuchs[22] conditions.

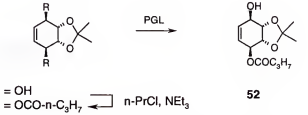
Reduction of **40** to the vinylsilane **41** was accomplished by partial catalytic hydrogenation to produce an inseparable 20:1 mixture of Z/E isomers. Removal of the silyl ether protecting group yielded alcohol **42**, which was oxidized to afford aldehyde **43**. In the key step, vinyl-silane-aldehyde **43** was treated with boron trifluoride etherate to furnish conduritol-A derivative **44** in 86% yield.

A chemoenzymatic synthesis of conduritol-A **10** was reported by Hudlicky et al. in 1991.[23] Enone **46** was obtained in 88% overall yield by protection of diol **45** as an acetonide, followed by singlet-oxygen addition and cleavage of the peroxide-bond with thiourea. Protection of the alcohol in **46** as a TBS-ether gave **47** in 85% yield. TBS-ether **47** was reduced with sodium borohydride to give a 1:1 mixture of alcohols **48** and **49**. After separation, isomer **49** furnished conduritol-A **10** upon acidic hydrolysis.



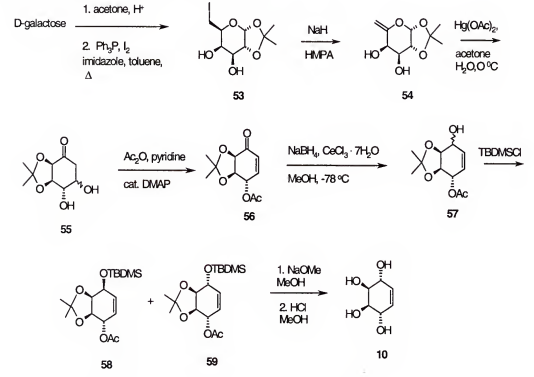
Scheme 8. The synthesis of conduritol-A by Hudlicky.

The Vanderwalle group reported an approach toward a homochiral derivative of conduritol-A in 1992.[24] Diol **50** was desymmetrized by *pseudomonas* glumae lipase (PGL) to give the protected conduritol-A derivative **52** in 85% yield with an ee of >95%.



Scheme 9. Vanderwalle's approach towards conduritol-A.

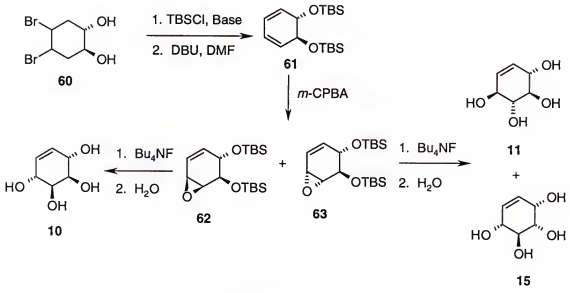
Mereyala and Gaddam performed a stereoselective synthesis of conduritol- A **10** from D-galactose in 1994 (Scheme 10).[25]



Scheme 10. The synthesis of conduritol-A by Mereyala

D-galactose was converted to 6-deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **53** with Ph_3P, I_2 and imidazole in toluene at reflux in 82% yield. Iodide **53** was treated with NaH in hexamethylphosphoric triamide (HMPA) at room temperature to afford 5,6-enopyranose **54** in 91% yield. Compound **54** was reacted with a catalytic amount of $Hg(OAc)_2$ in an acetone-water (2:1) mixture to yield derivative **55** in 83% yield. Diol **55** was reacted with Ac_2O-pyridine to afford the α–β-unsaturated enone **56** in 73% yield. The enone **56** was reduced under Luche conditions with $CeCl_3 7H_2O$-$NaBH_4$ to give the alcohol **57** as an isomeric mixture (1:3 α–alcohol/β–alcohol). The acetate **57** was treated with *tert*-butyldimethylsilyl chloride-pyridine to give silyl derivatives **58** and **59.** Acidic hydrolysis afforded conduritol-A **10** and conduritol-C **12.**

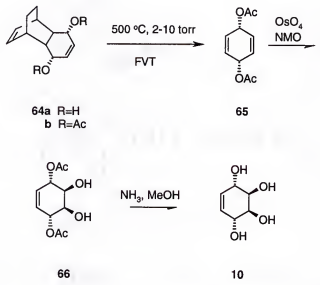
Billington and coworkers developed the synthesis of conduritol-A starting from the dibromodiol **60** in 1994 (Scheme 11).[26]



Scheme 11. Billington's synthesis of conduritol-A

Protection of dibromodiol **60** as the bis-TBS ether, followed by base catalyzed elimination gave the protected diene **61**. Treatment with peroxy acid gave a 1:1 mixture of epoxides **62** and **63**, which were separable by chromatography. The protecting groups were removed and opening of epoxide **62** afforded conduritol-A **10**, while opening of epoxide **63** afforded a 1:1 mixture of conduritols-B **11** and -F **15**.

In 1995, Zwanenburg and coworkers developed an efficient synthesis of conduritol-A **10** from *meso*-tricyclo[6.2.1.0]undecadien-3,6-diol which was obtained from the sodium borohydride reduction of tricyclo[6.2.1.0]undecadiene-dione (Scheme 12).[27]

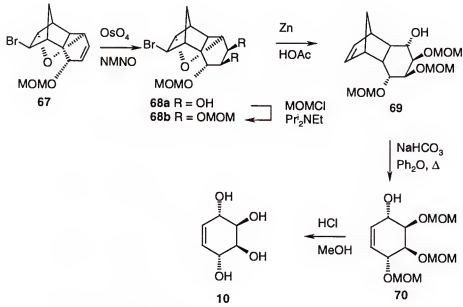


Scheme 12. Zwanenburg's approach to conduritol-A.

Diol **64a** was acylated with acetic anhydride to give the diacetate **64b**, which was subjected to flash vacuum thermolysis (FVT) at 500 °C to give 1,4-cyclohexadiene **65.** A stereoselective bishydroxylation of one of the olefinic bonds was achieved with a catalytic amount of osmium tetroxide in the presence of N-

methyl morpholine N-oxide to give the diol **66**. The diacetates were removed with ammonia in methanol to give conduritol-A **10**.

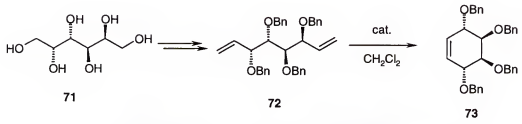
In 1999, the Ogasawara group published a paper describing the synthesis of all six conduritol isomers from the same Diels-Alder derived building block.[28] Their approach towards conduritol-A is shown in Scheme 13. Bromoene **67**[29] was hydroxylated with OsO_4 in 94% yield. Protection of the hydroxyl groups as MOM-ethers gave **68b** in 95% yield. Reductive cleavage of the bridged system furnished alcohol **69** in 91% yield, which was converted to cyclohexenol **70** by thermolysis in a yield of 93%. Removal of the protecting groups yielded conduritol-A **10** in quantitative yield.



Scheme 13. Ogasawara's synthesis of conduritol-A.

Furstner used ring-closing metathesis to access several protected conduritol isomers.[30] Galactitol **71** was converted in five steps to diene **72** in 30% overall yield. The latter smoothly underwent ring-closing metathesis in the presence of either

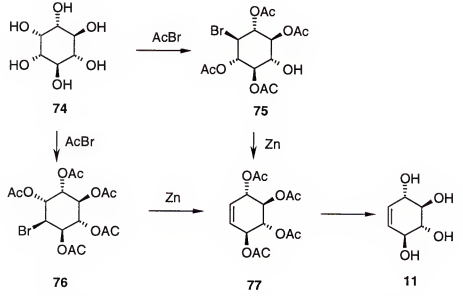
Schrock's molybdenum catalyst[31] or the ruthenium catalyst developed in Grubbs' laboratory[32] to furnish tetra-*O*-benzyl conduritol-A **73** in >90% yield.



Scheme 14. Furstner's synthesis of tetra-*O*-benzyl conduritol-A.

2.1.3 Conduritol-B

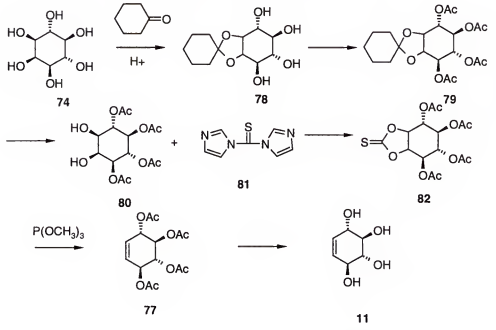
In 1907, Muller observed that penta-acetate of 6-bromoquercitol on treatment with zinc in acetic acid gave a product that analyzed for $C_{14}H_{18}O_6$.[33] Muller never reported the structure. Later McCasland repeated the experiment and verified it was Conduritol-B.



Scheme 15. McCasland's synthesis of conduritol-B.

McCasland and Horswill synthesized conduritol-B **11** from *myo*-inositol in 1953 (Scheme 15).[34] *Myo*-inositol **74** was treated with acetyl bromide to afford two bromoquercitol penta-acetates **75** and **76**. The penta-acetates were debrominated using zinc to give tetraacetate **77**. Deacetylation of the **77** gave conduritol-B **11**.

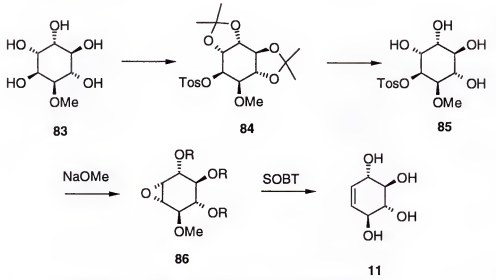
Nakajima et al. synthesized conduritol-B **11** in a mixture of conduritol-A **10** and E **14** in 1957 (Scheme 2).[14] In 1970, Nagabhushan developed a synthesis of conduritol-B from 1,4,5,6-tetra-O-acetyl*myo*-inositol **14** (Scheme 16).[35]



Scheme 16. Nagabhushan's synthesis of conduritol-B.

Myo-inositol **74** was reacted with cyclohexanone to yield ketal **78**. The ketal **78** was acetylated to give tetra-acetate **79** and subsquently hydrolyzed afforded diol **80**. Nagabhushan treated **80,** under Corey-Winter conditions, with N,N-thiocarbonyldiimidazole to afford the thiocarbonate **82**. Thiocarbonate **82** was treated with trimethylphosphite to afford tetraacetate **77**. Tetraacetate **77** was treated with triethylamine to give conduritol-B **11.**

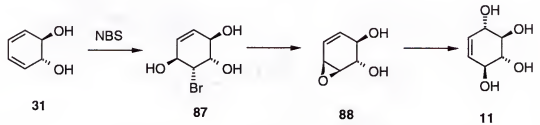
Paulsen and coworkers achieved the first enantioselective synthesis of conduritol-B **11** in 1981 (Scheme 17).[36] Quebrachitol **83** was protected as its diacetonide and tosylated to give compound **84**. Deprotection of **84** produced tosylate **85**. Upon treatment with sodium methoxide, **85** was converted to epoxide **86**. Using 3-methyl-2-(selenoxo)benzothiazole (SOBT), reductive deoxygenation and deprotection of **86** afforded (-)-conduritol B **11** in high yield.



83 **84** **85** **86** **11**

Scheme 17. Paulsen's synthesis of conduritol-B.

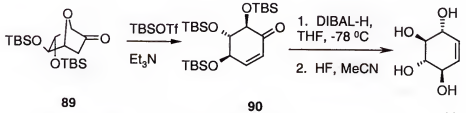
In 1985, Berchtold and Alwksjezh developed an efficient synthesis of conduritol-B **11** (Scheme 18).[17] Starting from dihydrobenzene diol **31**, treatment with *N*-bromosuccinimide in aqueous tetrahydrofuran gave bromide **87**. Debromination of **87** gave epoxide **88** and hydrolysis gave conduritol-B **11.**



31 **87** **88** **11**

Scheme 18. Berchtold's synthesis of conduritol-B.

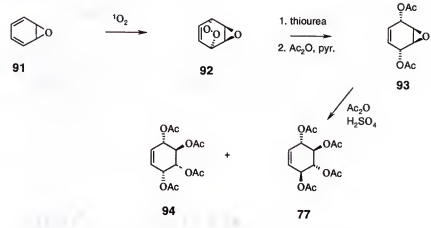
In 1989, Vogel and coworkers reported a Diels-Alder approach to enantioselective synthesis of (-)-conduritol-B **11**.(Scheme 19).[37] Ring opening of cyclic ether **89** with *tert*-butylsilyl triflate afforded enone **90**. Reduction of enone **90** using DIBAL-H and deprotection of the *tert*-butylsilyl groups gave (-)-conduritol-B **11**.



89 90 11

Scheme 19. Vogel's synthesis of conduritol-B.

In 1990, the Balci group reported the synthesis of a conduritol-B derivative.[38]

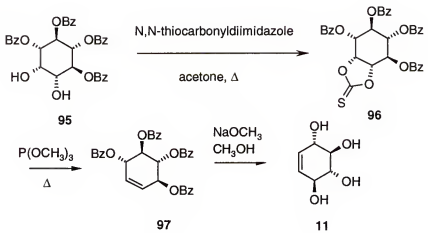


91 92 93 94 77

Scheme 20. Balci's synthesis of conduritol B derivative

Benzene-oxide **91** was converted to endoperoxide **92** according to a known procedure.[39, 40] Reductive cleavage of the peroxide followed by acylation of the alcohols provided cyclohexene derivative **93**. Ring-opening under acidic conditions afforded a 2:1 mixture of the tetraacetates of conduritol-F **94** and conduritol-B **77** in a combined yield of 67%.

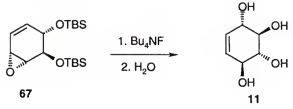
In a similar pathway to Nagabhushan's synthesis,[35] Ozaki and coworkers performed the first synthesis of (+)-conduritol-B starting from L-Quebrachitol in 1993 (Scheme 21).[41]



Scheme 21. Ozaki's synthesis of (+)-conduritol-B.

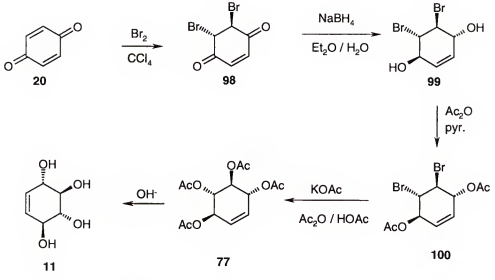
L-Quebrachitol was transformed into D-3,4,5,6-tetra-*O*-benzoyl-*myo*-inositol **95**. Compound **95** was treated with *N,N*-thiocarbonylimidazole to afford thiocarbonate **96**. Thiocarbonate **96** was reacted with trimethyl phosphite to give the protected conduritol **97**. Treatment of **97** with sodium methoxide gave (+)-conduritol-B **11**.

Billington and coworkers prepared conduritol-B **11** in 1994 as a by-product of the synthesis of conduritol-A **10**.[26] Epoxide **67** was treated with fluoride and hydrolyzed to afford conduritol-B **11**.



Scheme 22. Billington's synthesis of conduritol-B

An improved procedure for the synthesis of racemic conduritol-B was described in 1994 by the Taylor group.[42]

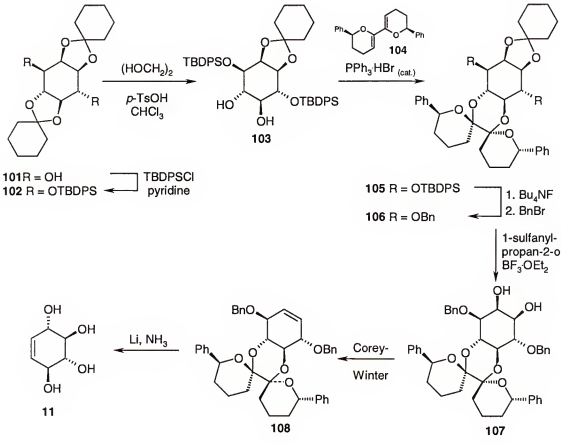


Scheme 23. Taylor's synthesis of conduritol-B

Benzoquinone **20** was brominated to give enone **98**, which was subsequently reduced to afford diol **99**. Acetylation of the diol furnished conduritol-B tetraacetate **77**, which was deprotected to give conduritol-B **11**.

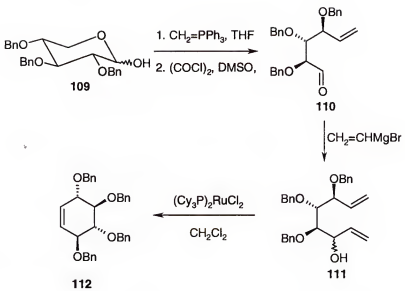
In 1997, Ley and coworkers reported the synthesis of (+)-conduritol-B **11** starting from a *myo*-inositol derivative.[43] 1,2:4,5-di-*O*-Cyclohexylidene-*myo*-inositol **101** was converted to the TBDPS-ether **102** in 72% yield. Cleavage of one of the acetals furnished **103** in 76% yield. Reaction of **103** with (2*S*, 2'*S*)-2,2'-diphenyl-6,6'-bi(3,4-dihydro-2*H*-pyran) **104** allowed for protection of the free hydroxyl groups as well as resolution in one step to give chiral species **105** in 35% yield. After switching the protecting groups from TBDPS to benzyl (61%), the cyclohexylidene acetal was selectively cleaved to give diol **107** in quantitative yield. Corey-Winter

deoxygenation of **107** provided olefin **108** in 97% yield, which, after removal of all protecting groups, furnished (+)-conduritol-B **11** in quantitative yield.



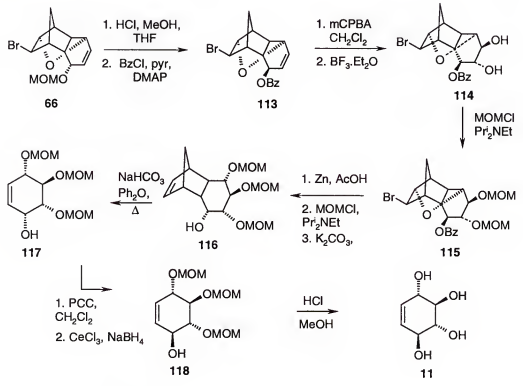
Scheme 24. Ley's synthesis of (+)-conduritol-B

Kornienko and D'Alarcao reported a ring-closing metathesis synthesis of a protected conduritol-B derivative in 1999.[44] Xylose derivative **109** was converted into enal **110** by Wittig-olefination and subsequent oxidation. Grignard addition to **110** gave a mixture of two diasteriomeric alcohols, the ratio of which could be varied from 8:1 to 1:3 by choice of conditions. After separation of the two products, the α-isomer of **111** was subjected to metathesis conditions to give tetra-*O*-benzyl conduritol-B **112** in 95% yield.



Scheme 25. D'Alarcao's synthesis of tetra-*O*-benzyl conduritol-B

Using the same building block as for conduritol-A **10**, the Ogasawara group synthesized conduritol-B **11** in 1999.[28]

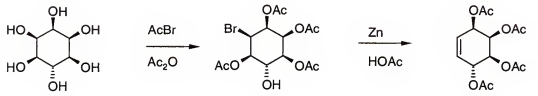


Scheme 26. Ogasawara's synthesis of conduritol-B

Ether **67** was deprotected under acidic conditions in 91% yield. Benzoylation of the alcohol gave benzoate **113** in 99% yield. Epoxidation of the double bond in 91% yield, followed by ring-opening under acidic conditions led to diol **114** in 76% yield. The hydroxyl groups in **114** were protected as MOM-ethers to give ether **115** in 97% yield. After cleavage of the ether bridge (99%), the resulting alcohol was protected as a MOM-ether in 82% yield and the benzoate hydrolyzed under basic conditions to afford alkene **116** in 94% yield. Thermolysis of **116** led to cyclitol **117** in 96% yield, which, after oxidation, reduction and cleavage of the protecting groups, gave conduritol-B **11** in 87% yield over three steps.

2.1.4 Conduritol-C

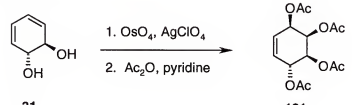
The first synthesis of conduritol-C **12** was achieved by McCasland and Reeves in 1955 (Scheme 27).[45] McCasland used a similar synthetic pathway in the synthesis of conduritol-B **11**. *epi*-Inositol **119** was reacted with acetyl bromide and acetic anhydride to afford bromoquercitol pentaacetate **120**. Pentaacetate **120** was transformed to tetraacetate **121** upon treatment of zinc-acetic acid. Conduritol-C **12** was obtained after hydrolysis. McCasland established the configuration of conduritol-C **12** by hydrogenation giving a saturated tetrol.



119 **120** **121**

Scheme 27. McCasland's synthesis of conduritol-C.

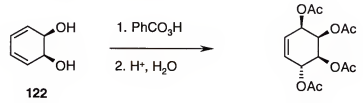
Nakajima and Tomida synthesized conduritol-C starting from *trans*-benzenediol **31** (Scheme 28).[14] The benzenediol **31** was dihydroxylated with osmium tetroxide in the presence of silver perchlorate. Acetylation gave the identical tetraacetate **121** reported by McCasland.[35]



31 **121**

Scheme 28. Nakajima's synthesis of conduritol-C derivative

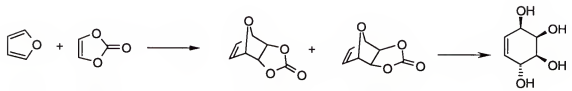
In 1985, Berchtold and Alwksjezh synthesized a derivative of conduritol-C.[17] *Cis*-diol **122** was treated with perbenzoic acid to give an epoxide, which could be hydrolyzed to furnish conduritol-C tetraacetate **121**.



122 **121**

Scheme 29. Berchtold's synthesis of conduritol-C tetraacetate

In 1961, Yurev and Zefirov achieved a stereospecific pathway to conduritol-C (Scheme 30).[46]

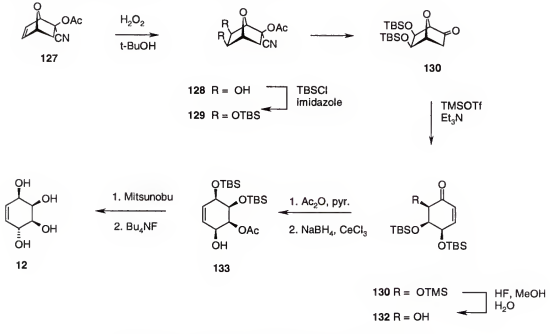


123 **124** **125** **126** **12**

Scheme 30. Yurev and Zefirov's synthesis of conduritol-C

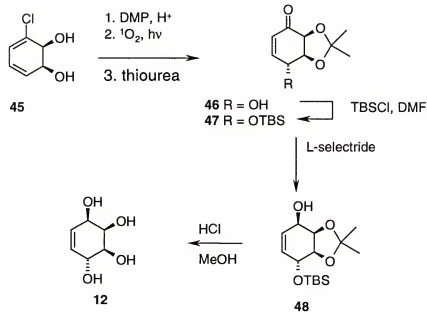
By means of a [4+2]cycloaddition of furan **123** and ethylene-carbonate **124**, *endo*- adduct **125** and *exo* adduct **126** were prepared. Hydroxylation of **125** and **126** under acid conditions and cleavage of the carbonate under basic conditions afforded conduritol-C **12**.

In 1989, Vogel and coworkers, using the same starting material employed for the synthesis of conduritol-B **12**, achieved the first total synthesis of optically pure (-)-conduritol-C.[37] Nitrile **127** was dihydroxylated to afford diol **128** in 58% yield. After silyl protection of the hydroxyl groups (36%), saponification furnished ketone **130** (80%). Ring-opening with TMSOTf afforded **131** (36%), followed by removal of the TMS group to give alcohol **132** in 71% yield. The latter was converted to its acetate derivative (95%) and subjected to Luche-reduction conditions to give all-*cis* alcohol **133** (92%). Mitsunobu inversion of **133** (87%), followed by deprotection with fluoride ion gave conduritol-C **12** in 71% yield.



Scheme 31. Vogel's synthesis of (-)-conduritol-C.

Hudlicky and coworkers reported a synthesis of (-)-conduritol-C from chlorobenzene dihydro-*cis*-diol in 1991.[47]

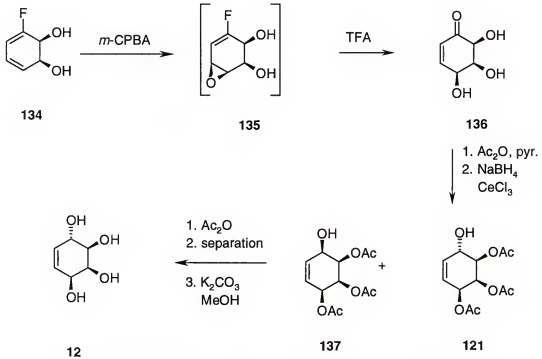


Hudlicky's synthesis of (-)-Conduritol-C.

Chiral diol **45** was protected as an acetonide, subsequent photooxidation and reduction gave enone **46** in 88% overall yield. After protection of the alcohol as its silyl ether (85%), the latter was reduced with L-selectride to furnish enol **48** (52%). Removal of the protecting groups under acidic conditions furnished (-)-conduritol-C **12**.

In 1991, Carless and Oak reported the first synthesis of (+)-conduritol-C **12**.[48] Chiral fluorodiol **134** [49] was epoxidized with *m*CPBA in the presence of trifluoroacetic acid to give epoxide **135** which was transformed into the triol **136** in 25% overall yield. Acetylation followed by Luche-reduction produced a 2:1 mixture of conduritol-C **121** and conduritol-D **137** derivatives in 78% overall yield. The

products were separated after acetylation (95%) and deprotected using potassium carbonate in methanol to afforded (+)-conduritol-C **12** in 88% yield.

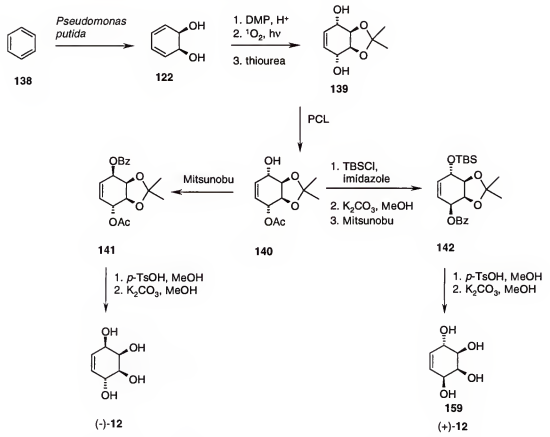


Scheme 33. Carless's synthesis of (+)-conduritol-C.

In 1991, Johnson and coworkers reported a chemoenzymatic approach which allowed access to both enantiomers of conduritol-C.[50]

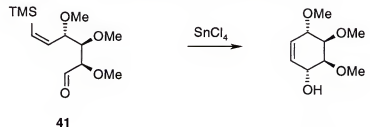
Biooxidation of benzene with *Pseudomonas putida* afforded diol **138**, which was converted to its acetonide in 82% yield. Singlet oxygen addition and subsequent reduction furnished diol **139** in an overall yield of 58%. Desymmetrization of **139** was achieved by acetylation with lipase from *Pseudomonas cepacia* to give alcohol **140** in 90% yield. For the synthesis of (-)-conduritol-C **12**, alcohol **140** was subjected to Mitsunobu conditions, followed by removal of all protecting groups to give (-)-**12** in 84% overall yield. The (+)-isomer was obtained by protection of the free OH-group in

140 as its silyl ether, removal of the acetate and inversion of the free alcohol to give alkene **142**. Deprotection afforded (+)-conduritol-C **12**.



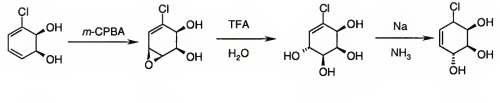
Scheme 34. Johnson's synthesis of conduritol-C enantiomers

Also in 1991, the Weinreb group used their vinylsilane-aldehyde cyclization methodology to obtain a conduritol-C derivative. In the key step, vinylsilane **41** was treated with $SnCl_4$ to give conduritol-C derivative **143** in 68% yield.



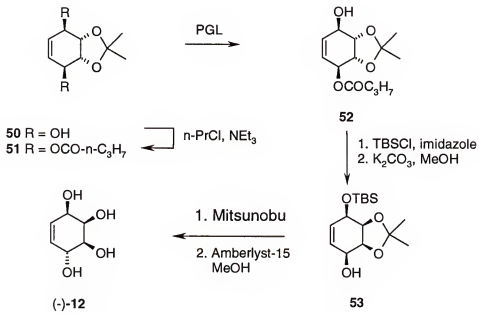
Scheme 35. Weinreb's synthesis of conduritol-C derivative.

In 1992, Carless used chlorobenzene dihydro-*cis*-diol in the synthesis of the (-)-enantinomer.[51] Epoxidation of diol **45** with *m*CPBA afforded epoxide **144** in 61% yield. Acid-catalyzed hydrolysis of **144** afforded tetrol **145** in 66% yield. The tetrol was treated with sodium in liquid ammonia to give (-)-conduritol-C **12** in 70% yield.



Scheme 36. Carless's synthesis of (-)-conduritol C

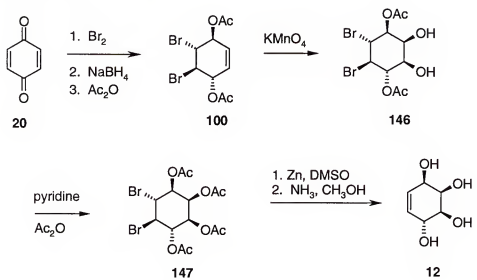
The Vanderwalle group reported their synthesis of (-)-conduritol-C **12** in 1992.[52]



Scheme 37. Vanderwalle's synthesis of (-)-conduritol C.

Diol **50** was converted to di-*n*-propyl ester **51** and desymmetrized with lipase (PGL) to give mono-ester **52** in 83% yield. TBS protection of the alcohol, followed by saponification of the ester gave allylic alcohol **53** in 97% yield. Inversion of the free hydroxyl using Mitsunobu conditions followed by acidic hydrolysis furnished (-)-conduritol-C **12** in 90% yield.

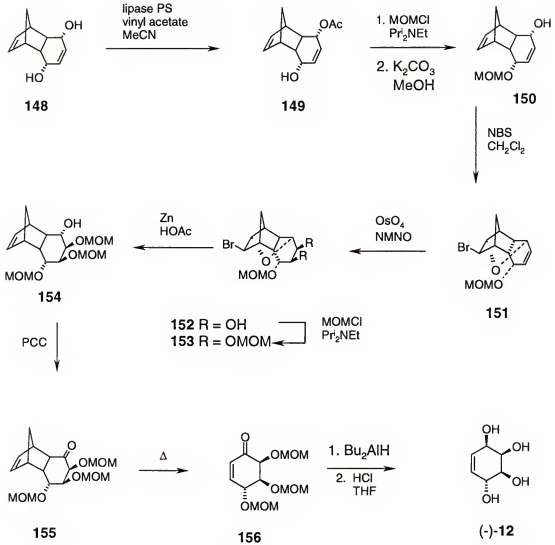
In 1992, the Balci group developed a synthesis for conduritol-C starting from benzoquinone **20** (Scheme 38).[53]



Scheme 38. Balci's synthesis of conduritol-C

Bromination of benzoquinone **20** followed by reduction and acetylation gave dibromide **100**. *cis*-Hydroxylation of **100** with $KMnO_4$ afforded the *cis*-diol **146**. Acetylation of **146** followed by treatment with zinc in DMSO gave the tetraacetate **147** which afforded conduritol-C **12** after ammonolysis.

Takano and coworkers published their synthesis of conduritol-C in 1993.[54] Diels-Alder adduct **148** was resolved by lipase-assisted acylation in 87% yield.

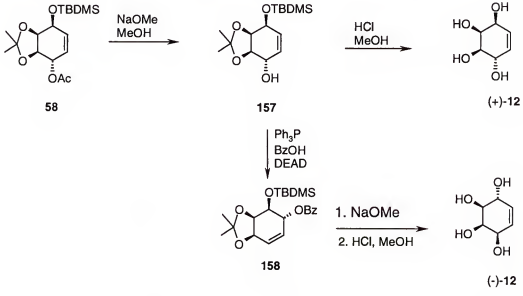


Scheme 39. Takano's synthesis of conduritol-C

Protection of the remaining hydroxyl group as the MOM-ether in 88% yield and removal of the acetate gave compound **150**. Bromination of **150** with NBS afforded bromoether **151** in 67% yield over two steps. The bromoether was dihydroxylated to give diol **152** in 85% yield. Protection of the OH-groups as MOM-ethers gave **153**, which was debromintated to give olefin **154** in 77% yield. Oxidation of the hydroxyl group in **154**, followed by a retro-Diels-Alder reaction gave enone

156 in 60% yield. Selective reduction and removal of the MOM-ethers yielded (-)-conduritol-C **12** in 84% yield.

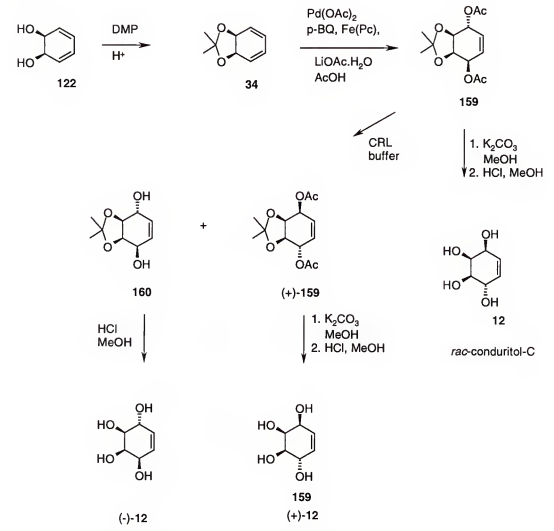
Mereyala and Gaddam reported the synthesis of both isomers of conduritol-C in 1994.[25] Acetate **58** was deprotected under basic conditions to give alcohol **157**, which upon acidic hydrolysis gave (+)-conduritol-C **12**. Alcohol **157** was subjected to Mitsunobu conditions to afford benzoate **158**. Deprotection of **158** furnished (-)-conduritol-C **12** in 63% overall yield.



Scheme 40. Mereyala's synthesis of conduritol-C enanatiomers

In 1998, Backvall and Yoshizaki published an approach towards both isomers of conduritol-C.[55, 56] Diol **122** was converted to its acetonide in 86% yield. Palladium-catalyzed *trans*-1,4-diacetoxylation furnished alkene **159** in 71% yield. The alkene was then deprotected to give racemic conduritol-C **12** in 88% yield. The racemic diacetate **159** was subjected to enzymatic resolution to give diol **160** and chiral diacetate (+)-**159**, respectively in 49% yield. Both of these compounds could

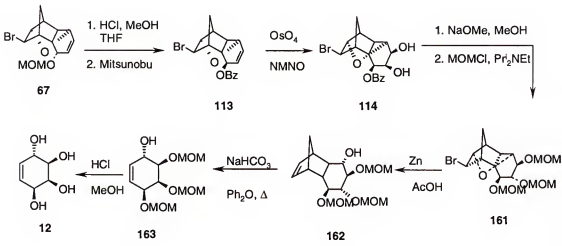
then be deprotected to give (+)- **12** and (-)-**12** conduritol-C in 98% and 99% yield, respectively



Scheme 41. Backvall's synthesis of conduritol- C enantiomers

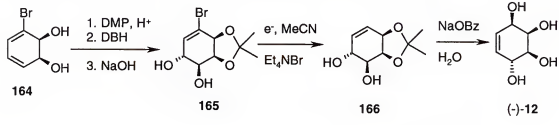
The Ogasawara group reported a synthesis of conduritol-C in 1999.[57] Alkene **67** was deprotected under acidic conditions in 91% yield. Mitsunobu conditions led to the inversion of the hydroxyl group to furnish benzoate **113** in 86% yield. Di-hydroxylation of alkene **113** provided diol **114** in 97% yield. Hydrolysis of the benzoate was followed by protection of the hydroxyl groups as the corresponding MOM-ethers to produce **162** in 89% yield. Reductive cleavage of the ether bridge,

followed by thermolysis afforded alcohol **163** (84%), which, after deprotection, gave conduritol-C **12** in 93% yield.



Scheme 42. Ogasawara's synthesis of conduritol-C

Hudlicky and coworkers reported a "reagent-free" synthesis of conduritol-C in 1999.[58] Diol **164** was protected as its acetonide and subsequently transformed to *trans*-diol **165**. The *trans*-diol was subjected to electrochemical reduction to remove the halogen. Hydrolysis of the acetonide gave (-)-conduritol-C **12**.

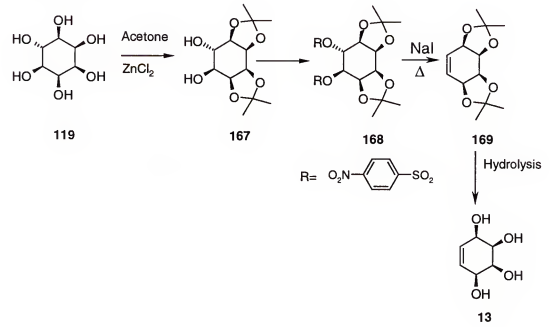


Scheme 43. Hudlicky's synthesis of (-)-conduritol-C

2.1.5 Conduritol-D

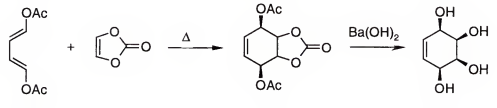
The first synthesis of conduritol D **13** was achieved by Angyal and Gilham in 1955, starting with an *epi*-inositol derivative (Scheme 44).[59] *Epi*-inositiol **119** was

transformed into di-acetonide **167**. Di-acetonide **167** was then protected with a nitrobenzenesulfonyl group to afford **168**. Elimination at 100 ^{0}C afforded the acetonide protected derivative of conduritol-D **169**. Hydrolysis of **169** gave conduritol-D **13**.



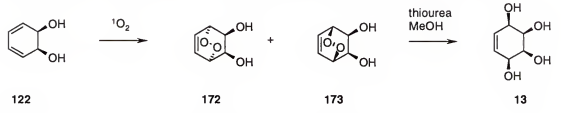
Scheme 44. Angyal's synthesis of conduritol-D

Criegee and Becher used a Diels-Alder approach to obtain conduritol-D **13** in 1957 (Scheme 45).[60] Reaction of *trans-trans*-diacetoxybutadiene **170** with ethylenecarbonate **124** at high temperature and pressure yielded compound **171**. Saponification of **171** with $Ba(OH)_2$ afforded conduritol-D **13**.



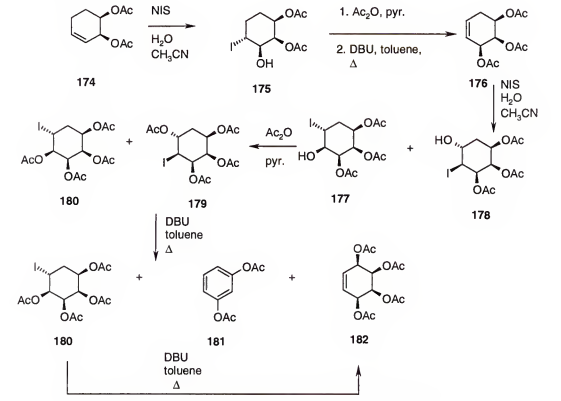
Scheme 45. Criegee's synthesis of conduritol-D

Carless and Oak reported a chemoenzymatic approach towards conduritol-D **13** in 1989.[19] Diol **122**, obtained by microbial oxidation of benzene, was exposed to singlet-oxygen giving a mixture of peroxides **172** and **173**. After separation, **173** could be converted to conduritol-D **13** by reduction with thiourea in methanol.



Scheme 46. Carless's synthesis of conduritol-D

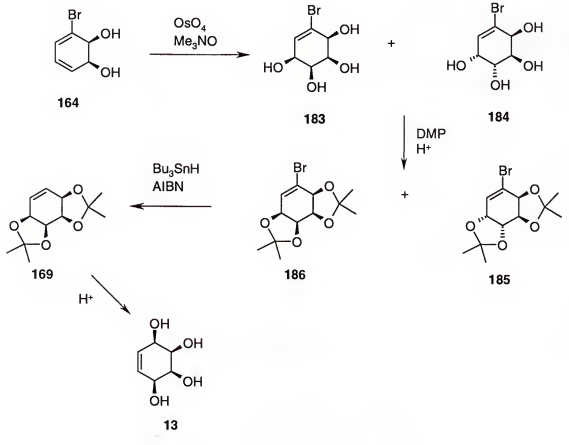
In 1996, the Sweeney group reported the synthesis of a tetraacetate derivative of conduritol-D **182**.[61, 62]



Scheme 47. Sweeney's synthesis of conduritol-D

Diacetate **174** was subjected to hydroxyiodination to give alcohol **175** (60%), which was converted to alkene **176** by acetylation and subsequent elimination in 63% yield. The hydroxyiodination of **176** gave a 1:2.3 mixture of alcohols **177** and **178**, respectively. Both alcohols were acetylated to give tetraacetates **179** and **180** in 53% overall yield. Reaction of the mixture with DBU afforded conduritol-D tetraacetate **182** in 26% yield along with aromatized product **181** and starting material **180**, which could be converted to conduritol-D tetraacetate **182**.

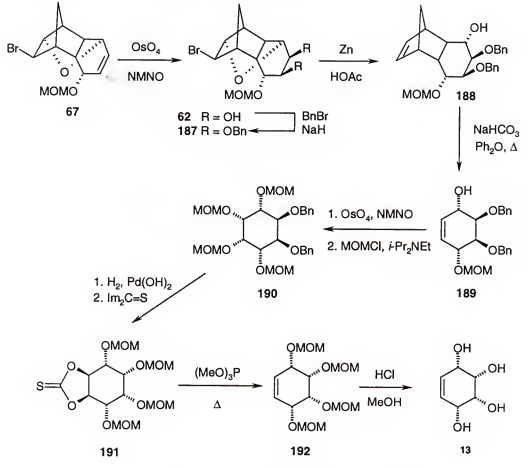
Donohoe and co-workers reported their synthesis of conduritol-D **13** in 1997.[63]



Scheme 47. Donohoe's synthesis of conduritol-D

Diol **164** was oxidized, using a directed hydroxylation strategy,[64] to furnish diol **183** and **184** in yields of 83% and 18% yield, respectively. The diols were treated with dimethoxypropane and acid to give the acetonides **185** and **186**, the mixture was separated (90% total yield). The compound **186** was dehalogenated with TBTH to afford **169** in 96% yield. Acid hydrolysis of the acetonides gives conduritol-D **13** in 79% yield.

The Ogasawara group prepared conduritol-D **13** in 1999.[57] Osmylation of alkene **67** afforded the dihydroxylated product **62** in 97% yield.

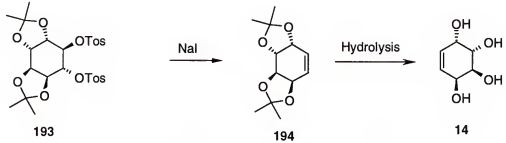


Scheme 49. Ogasawara's synthesis of conduritol-D

The hydroxyl groups were protected as benzyl ethers to afford compound **187** in 97% yield. Reductive cleavage gave alcohol **188** in 98% yield. Retro-Diels-Alder furnished allylic alcohol **189** in 90% yield. Directed osmylation of the alkene (96%), followed by MOM-protection gave cyclohexane derivative **190** in 96% yield. The benzyl ethers were hydrogenated to the diol and converted to thiocarbonate **191** (94%), which was subsequently deoxygenated to give alkene **192** in 97% yield. Hydrolysis of the acetonide gave conduritol-D **13** in quantitative yield.

2.1.6 Conduritol-E

The first stereospecific synthesis of conduritol-E **14** was reported by Angyal and Gilham in 1955 (Scheme 50).[59] The synthetic pathway is similar to the route employed for conduritol-D **13.** Di-*O*-tosylinositol **193** was treated with sodium iodide to give cyclohex-5-ene tetrol derivative **194**. Hydrolysis of **194** gave conduritol-E **14**.

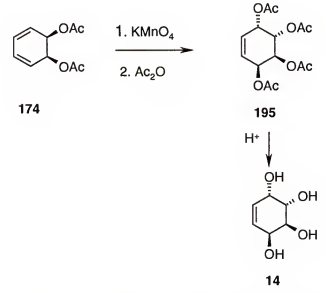


193 194 14

Scheme 50. Angyal's synthesis of conduritol-E

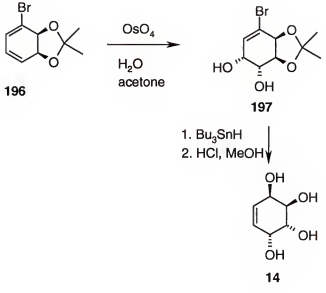
A non-stereospecific synthesis of conduritol-E **14** was also accomplished by the Nakajima laboratory in 1957.[14] Later, Nakajima published a stereospecific synthesis using *cis*-benzene diol diacetate.[65] Acetylated diol **174** was osmylated

followed by acetylation yielding tetraacetate **195**. Hydrolysis of **195** afforded conduritol-E **14**.



Scheme 51. Nakajima's synthesis of conduritol-E

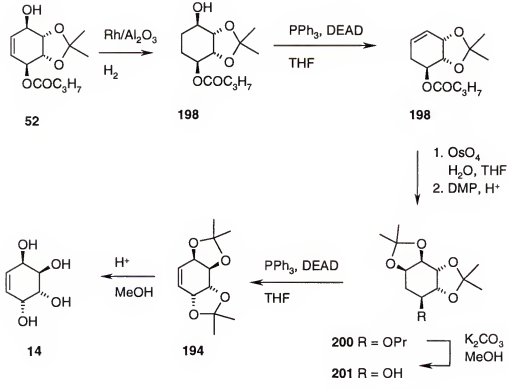
Hudlicky and co-workers published their synthesis of conduritol-E **14** in 1991.[66,67]



Scheme 52. Hudlicky's synthesis of conduritol-E

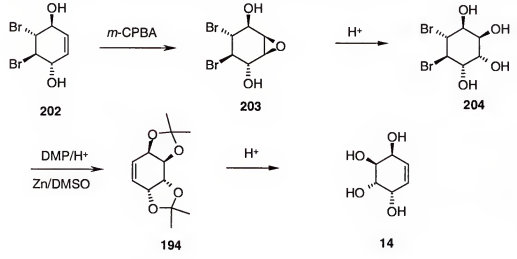
Acetonide **196** was dihydroxylated to give diol **197** in 85% yield. The dehalogenation of **197** using radical conditions was achieved in 85% yield. Deprotection under acidic conditions afforded (-)-conduritol-E **14** in 99% yield.

The Vanderwalle group published a synthesis of (-)-conduritol-E **14** from chiral alcohol **52** in 1992 (Scheme53).[52] Alcohol **52** was hydrogenated in 95% yield. Elimination of the alcohol furnished alkene **199** in 89% yield. Alkene **199** was hydroxylated and protected as an acetonide in 39% yield to give **200**. After removal of the propyl ester, **201** was dehydrogenatated with triphenylphosphine and DEAD to give cyclohexene derivative **194** in 89% yield. Hydrolysis of the acetonides afforded (-)-conduritol-E **14** in 85% yield.



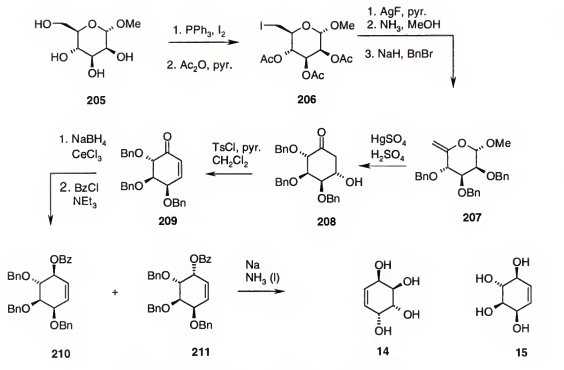
Scheme 53. Vanderwalle's synthesis of (-)-conduritol-E.

In 1992, the Balci group developed a synthesis of conduritol-E **14** (Scheme 54).[53,68] Dibromide **202** was treated with *m*-CPBA to give the epoxy compound **203**. Acid-catalyzed opening of the epoxide gave tetrol **204**. Tetrol **204** was protected as its di-acetonide, reduced, and hydrolyzed to yield conduritol-E **14**.



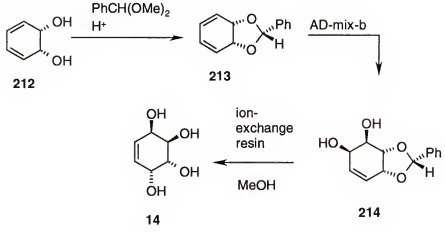
Scheme 54. Balci's synthesis of conduritol-E

The Chapleur group prepared (-)-conduritol-E **14** from a D-mannose derivative in 1993[69] (Scheme 55). The primary alcohol of methyl-α-D-*manno* pyranoside **205** was iodinated, then acetylatated to give iodide **206** in 91% yield. Silver fluoride elimination of HI, followed by removal of the acetates and protection of the alcohols as benzyl ethers gave **207** in 83% yield. Ferrier-rearrangement of **207** led to cyclohexanone derivative **208** in 80% yield. Compound **208** was subjected to elimination to afford unsaturated ketone **209** in 82% yield. Luche-conditions gave two isomeric alcohols which were benzoylated to produce **210** and **211** in yields of 20% and 71%, respectively. Deprotection of **211** with sodium in liquid ammonia yielded (-)-conduritol-E **14** in 72% yield.



Scheme 55. Chapleur's synthesis of conduritol-E

Takano et al. used an asymmetric dihydroxylation approach in their synthesis of conduritol-E **14** in 1994 (Scheme 56).[70]

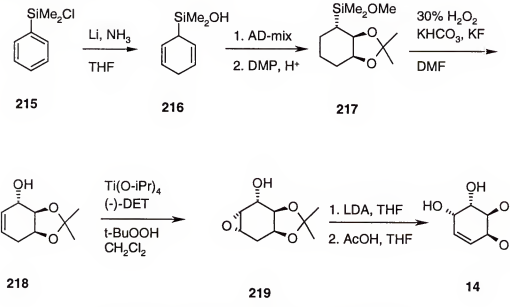


Scheme 56. Takano's synthesis of conduritol-E

Meso-diol **212** was converted to its benzylidene acetal in 72% yield. Compound **213** was then subjected to Sharpless' asymmetric hydroxylation

conditions to give diol **214** (60%), which could be deprotected with ion-exchange resin to produce conduritol-E **14** in 75% yield.

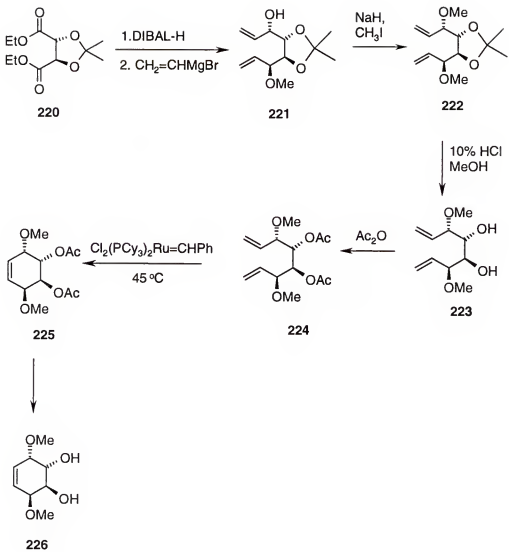
Landis and Angelaud developed an enantioselective synthesis of (+)-conduritol-E **14** in 1996 (Scheme 57).[71]



Scheme 57. Landis's synthesis of (+)-conduritol-E

Birch reduction of **215** gave 2,3-cyclohexadienylsilanol **216**. Dihydroxylation with AD-mix afforded a diol which was later protected as an acetonide **217**. Oxidation of **217** afforded the allylic alcohol **218**. Sharpless epoxidation of **218** gave the epoxy compound **219** which was opened using LDA and deprotected to give (+)-conduritol-E **14**.

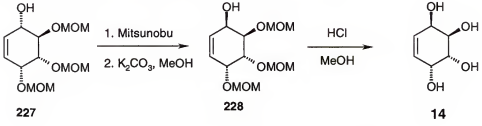
In 1999, Chang prepared a derivative of (+)-conduritol-E starting from a diethyl-L-tartrate derivative **220**.[72]



Scheme 58. Chang's synthesis of (+)-conduritol-E derivative

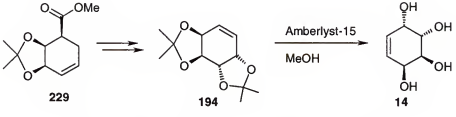
Partial reduction of **220** with DIBAL-H gave the dialdehyde which was treated in situ with vinylmagnesiumbromide affording a mixture of bis-allyl alcohol **221** and its diastereomers (77:23) in 54% yield. Methylation of the hydroxyl group, hydrolysis of the acetonide, and acetylation was achieved in 86% yield over 3 steps. Ring-closing olefin metathesis (RCM) of the dienyl compound **224** to cyclohexene derivative **225** was performed in 73% yield. Deacetylation was performed in quantitative yield to give conduritol-E derivative **226** (Scheme 58).

The Ogasawara group also published a synthesis of conduritol-E **14** in 1999.[57] Mitsunobu conditions inverted the hydroxyl in alkene **227**. Hydrolysis of the benzoate gave **228** in 70% yield. Deprotection of **228** under acidic conditions produced conduritol-E **14** in quantitative yield (Scheme 59).



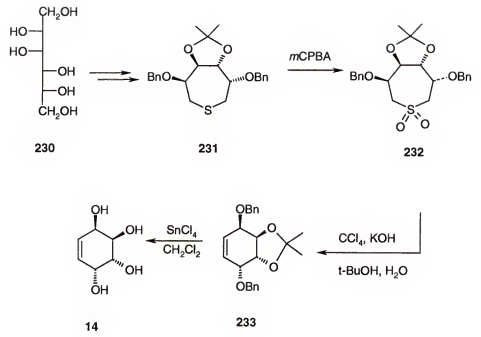
Scheme 59. Ogasawara's synthesis of conduritol-E

In 2000, the Mehta group reported a synthesis of conduritol-E **14**.[73] Ester **229** was converted to alkene **194**. Deprotection of **194** furnished conduritol-E **14** in 93% yield (Scheme 60).



Scheme 60. Mehta's synthesis of conduritol-E

In 2000, Cere and coworkers published a synthesis of (-)-conduritol-E **14**.[74,75] Thioether **231**, obtained from D-mannitol **230** by a known procedure,[76] was oxidized to the corresponding sulfone **232** (97%). The latter was subjected to a Ramberg-Bäcklund reaction to give cyclohexane derivative **233**, which could be deprotected to furnish (-)-conduritol-E **14** in 59% yield.

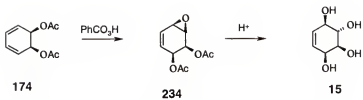


Scheme 61. Cere's synthesis of (-)-conduritol-E

2.1.7 Conduritol-F

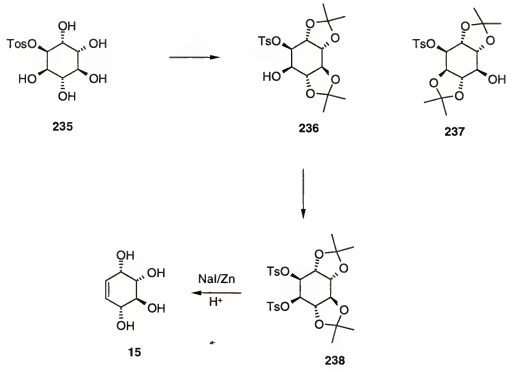
In 1962, Plouvier discovered a new optically active isomer of conduritol-A **10**.[77] This new isomer was isolated from *Crysanthemum Leucanthemitol.* Plouvier named the isomer L-Leucanthemitol which was later known as conduritol-F **15**. Conduritol-F **15** is found in almost all green plants. Plouvier incorrectly characterized the conduritol-F **15** as a solid. Later Paulsen corrected the characterization stating that it is an oil.[78] The first synthesis was achieved three years earlier by Nakajima and Tomida without knowing of its existence in nature.[14]

Protected *cis*-benzene diol **174** was oxidized to give epoxide **236**, which gave conduritol-F **15** after acidic hydrolysis.



Scheme 62. Nakajima's synthesis of conduritol-F

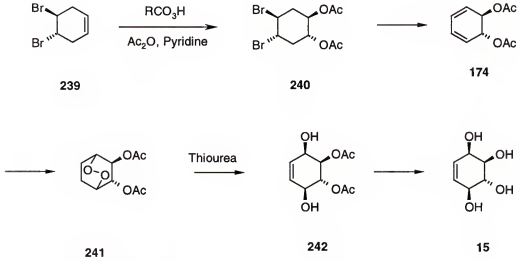
In 1981, Paulsen and coworkers achieved an enantioselective synthesis of conduritol-F **15** using a similar approach described for conduritol-B **11** and conduritol-E **14**.[36]



Scheme 63. Paulsen's synthesis of (-)-conduritol-F

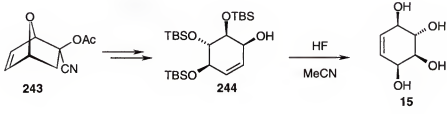
The tosylate of quebrachitol **277** was converted to diacetonide **236** and **237.** Compound **236** was treated with tosyl chloride followed by elimination with sodium iodide and zinc to provide conduritol-F derivative **238**. Deprotection of **238** gave (-)-conduritol-F **15**.

The Balci group developed a stereospecific pathway to conduritol-F **15** starting with dibromocyclohexadiene **239** in 1990 (Scheme 64).[38] Epoxidation and acetylation afforded diacetate **240**. Treatment of **240** with lithium chloride and lithium carbonate produced diacetate **174**. Photooxygenation of diacetate **179** afforded endoperoxide **241**. Selective reduction of the peroxide linkage with thiourea gave compound **242**. Deacetylation gave conduritol-F **15**.



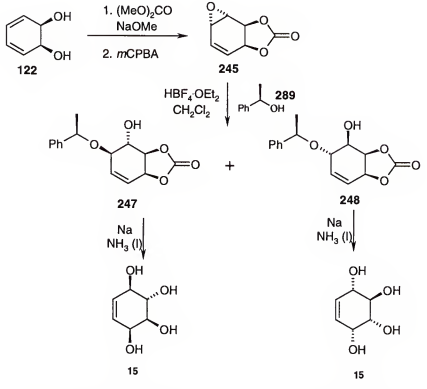
Scheme 64. Balci's synthesis of conduritol-F

Using the same approach that led them to conduritol-B **11**,[37] Vogel and coworkers were able to prepare (+)-conduritol-F **15** in 1990. Nitrile **243** was converted to alcohol **244** which could then be deprotected to furnish (+)-conduritol-F **15**.



Scheme 65. Vogel's synthesis of (+)-conduritol-F

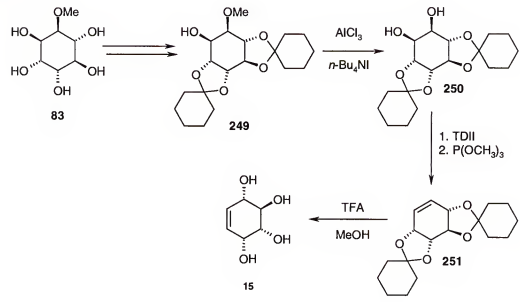
Ley and Redgrave prepared both enantiomers of conduritol-F **15** in 1990 (Scheme 66).[79] Diol **122** was transformed to its carbonate, then epoxidized to give vinyl oxirane **245** in 47% overall yield. Regioselective ring opening of **245** with (*R*)-*sec*-phenethyl alcohol **246** gave a 1:1 mixture of isomeric alcohols **247** and **248** (67%), which were deprotected to afford (+) and (-)-conduritol-F in yields of 80% and 85%, respectively.



Scheme 66. The synthesis of (+) and (-)-conduritol-F by Ley

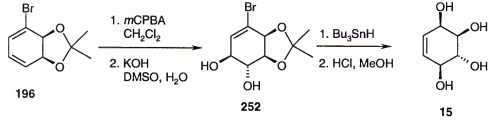
In 1991, Ozaki and coworkers reported the synthesis of the (-)-enantiomer of conduritol-F **15** from L-Quebrachitol.[80] L-Quebrachitol **83** was converted to alcohol **249**, which was treated with aluminum chloride and iodide to give diol **250** in 78% yield. Diol **250** was then converted to its thiocarbonate, which was treated with

trimethylphosphite to give cyclohexene derivative **251** in 90% for two steps. Deprotection of alkene **251** under acidic conditions furnished (-)-conduritol-F **15** in 90% yield.



Scheme 67. The synthesis of (-)-conduritol-F by Ozaki

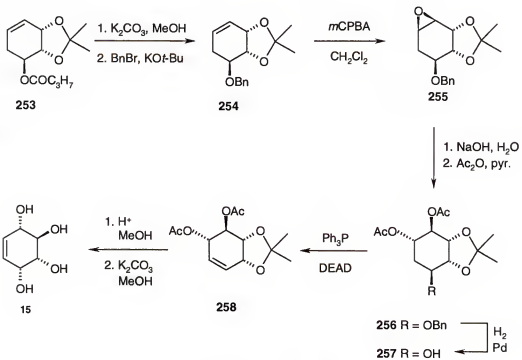
In 1991, the Hudlicky group reported a synthesis of (+)-conduritol-F **15** (Scheme 68).[66,67]



Scheme 68. Hudlicky's synthesis of (+)-conduritol-F

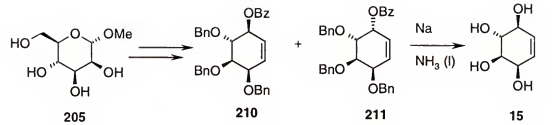
Acetonide **196** was epoxidized with *m*CPBA in 80% yield. Ring opening furnished *trans*-diol **252** in 63% yield. Debromination under radical conditions, followed by acidic deprotection, led to (+)-conduritol-F **15** in 99% yield.

In 1992, Vanderwalle reported the synthesis of (-)-conduritol-F **15** (Scheme 69).[52] Chiral ester **253** was converted to benzyl ether **254** in 80% yield. Epoxidation of the olefin furnished epoxide **255** in 83% yield. Ring opening of the epoxide and subsequent acetylation afforded diacetate **256** in 80% yield. After removal of the benzyl group the alcohol was subjected to Mitsunobu conditions, which resulted in elimination to give cyclohexene derivative **258** in 75% yield for two steps. Deprotection yielded (-)-conduritol-F **15** in 37% yield.



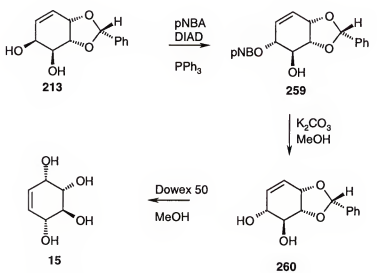
Scheme 69. Vanderwalle's synthesis of (-)-conduritol-F

In 1993, the Chapleur group reported a synthesis of (-)-conduritol-F **15** (Scheme 70).[81] D-mannose derivative **205** was transformed into two diastereomeric alcohols **210** and **211**, respectively. After separation, **210** was deprotected with sodium in liquid ammonia to afford (-)-conduritol-F **15**.



Scheme 70. Chapleur's synthesis of (-)-conduritol-F

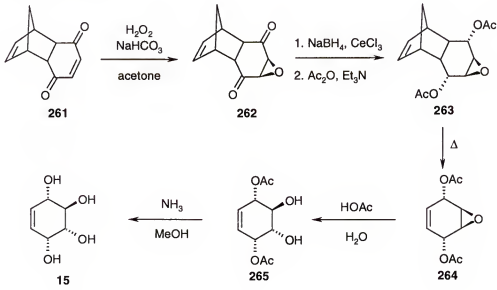
In 1995, the Ogasawara group reported a synthesis of (+)-conduritol-F **15**, starting from a conduritol-E derivative **213** (Scheme 71).[82] 1,2-*O*-Benzylidene conduritol-E **213** was subjected to Mitsunobu conditions and *p*-nitrobenzoic acid (*p*NBA) to give alcohol **259** in 79% yield. Removal of the *p*-nitrobenzoate furnished **260** in 81% yield, which upon treatment with ion-exchange resin gave (+)-conduritol-F **15** (80%).



Scheme 71. The synthesis of (+)-conduritol-F by Ogasawara

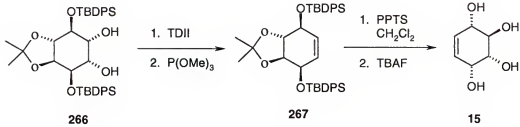
In 1995, Zwanenburg and coworkers reported a synthesis of conduritol-F **15**, starting from a Diels-Alder adduct **261** (Scheme 72).[27] Compound **261** was converted to epoxide **262** in 93% yield. Compound **262** was then reduced under Luche-

conditions to furnish a diol which was protected as di-acetate **263** in 81% yield over two steps. Thermolysis of **263** furnished epoxide **264**, which was opened with water to give diol **265** in 65% yield. Deprotection under basic conditions yielded conduritol-F **15** in quantitative yield.



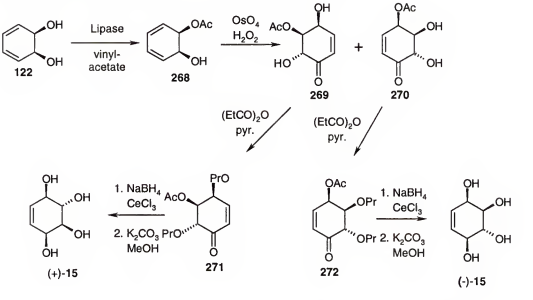
Scheme 72. Zwanenburg's synthesis of conduritol-F

Chiara and Valle reported their synthesis of (-)-conduritol-F **15** in 1995 (Scheme 73).[83] Diol **266** was subjected to Barton deoxygenation to afford cyclohexane derivative **267** in 79% yield. Treatment with TBAF afforded (-)-conduritol-F **15**.



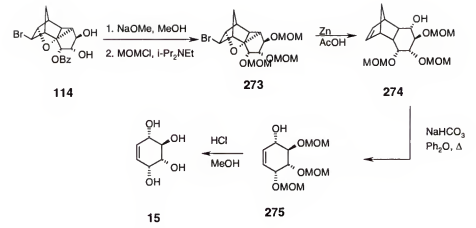
Scheme 73. The synthesis of (-)-conduritol-F by Chiara

Nicolosi and coworkers published an enantioselective synthesis of both isomers of conduritol-F **15** in 1996 (Scheme 74).[84] *Meso*-diol **122** was desymmetrized using an enzymatic acetylation, affording chiral alcohol **268** in 89% yield (>98% ee). Hydroxylation under Milas-conditions[85] produced a 3:2 mixture of diastereomers **269** and **270**. After acylation with propionic anhydride the mixture could be separated to give **271** and **272** in yields of 48% and 32%, respectively. Each isomer was subjected to Luche-reduction, followed by deprotection to afford (+) and (-)-conduritol-F **15** in yields of 90% and 88%, respectively.



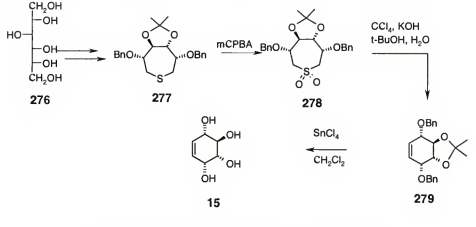
Scheme 74. The synthesis of (+)- and (-)-conduritol-F by Nicolosi

The Ogasawara group reported a synthesis of (-)-conduritol-F in 1999 using a Diels-Alder approach (Scheme 75).[27] The benzoate in **114** was removed under basic conditions followed by protection of the hydroxyls as MOM-ethers to furnish **273** in 92% yield. Reductive cleavage of the ether bridge furnished alkene **274** (91%), which was converted to cyclohexene derivative **275** by thermolysis in 77%. Deprotection under acidic conditions produced (-)-conduritol-F **15** in quantitative yield.



Scheme 75. The synthesis of (-)-conduritol-F by Ogasawara

The Cere group reported a synthesis of (-)-conduritol-F **15** using the same approach they had incorporated for the synthesis of conduritol-E (Scheme 76).[86,87]



Scheme 76. Cere's synthesis of (-)-conduritol-F

D-Sorbitol **276** was converted to thioether **277**. After oxidation of **277** to the sulfone in 87% yield, **278** was subjected to a Ramberg-Bäcklund reaction to give cyclohexene derivative **279** (79%), which was deprotected to give (-)-conduritol-F **15** in 77% yield.

2.2 Inositols

2.2.1 Introduction

Inositols have long been interesting compounds. Researchers were attracted to this field by the unique properties of the inositols, their stereochemical relationship, and the puzzling questions about their function in nature, as well as for their pharmaceutical benefit. More recently the inositols have been used as synthetic intermediates in natural product syntheses.

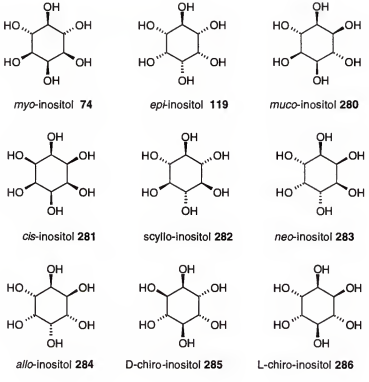


Figure 4

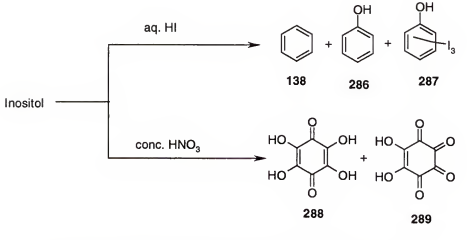
The stereochemical properties of the cyclohexane ring with six attached hydroxyl groups theoretically allow for the existence of 64 (2^6) isomers. However, after careful examination, it turns out that there exist only nine different compounds, while all other 54 possible isomers resemble one of these nine distinct structures.

Amazingly, this fact was already known over one hundred years ago, mainly due to the efforts of Bouveault.[88]

An overview of the nine inositols is given in Figure 4. Several excellent reviews[89-91] as well as monographs[92,93] concerning the inositols have appeared in the literature.

2.2.2 *Myo*-Inositol

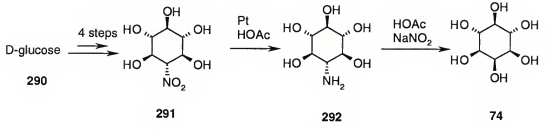
myo-Inositol is the most abundant of all the inositols. Since the other eight isomers are found so rarely it is common to refer to myo-inositol simply as inositol. In 1850 Scherrer discovered inositol in Liebig's meat extract.[94] In 1887, Maquenne proved the structure of inositol by treating *myo*-inositol **74** with hydriodic acid and thereby established a mixture of benzene **138**, phenol **286** and triiodophenol **287**.[95] Oxidation with concentrated nitric acid gave tetrahydroxy-*p*-benzoquinone **288** and rhodizonic acid **289**, another strong argument for the presence of a six-membered ring (Scheme 76). The distinct color of alkaline earth salts of quinine were used as a qualitative test for inositol.



Scheme 76. Marquenne's proof of the identity of inositol

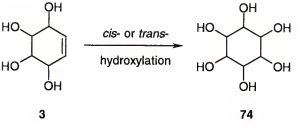
From these results, Marquenne concluded that inositol had to be a hexahydroxycyclohexane. These results were later confirmed by Wieland and Wishart, who found that catalytic reduction of hexahydroxybenzene gave more than 50% yield *myo*-inositol.[96]

The first total synthesis of *myo*-Inositol **74** was reported by Posternak in 1950.[97] Posternak prepared *myo*-inositol **74** from amino-dexoy inositol **292** which was prepared from D-glucose by a procedure by Fischer.[98]



Scheme 77. Posternak's synthesis of *myo*-inositol

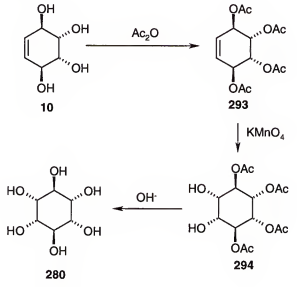
Later, Angyal identified myo-inositol along with several other inositols from the hydrogenolysis of hexabenzene.[99] Nakajima and coworkers synthesized all inositols excluding *cis*-inositol by hydroxylation of different conduritols (Scheme 78).[100] In 1983, Prinzbach prepared *myo*-inositol from dianhydroinositols obtained from benzene.[101]



Scheme 78. Nakajima's synthesis of inositols

2.2.3 *Muco*-Inositol

The first synthesis of *muco*-inositol **280** was described by Dangschat and Fischer in 1939 starting from conduritol-A **10** (Scheme 79).[10,11] Conduritol-A **10** was acetylated, followed by oxidation to furnish diol **294**. Hydrolysis of the ester groups gave *muco*-inositol **280**.

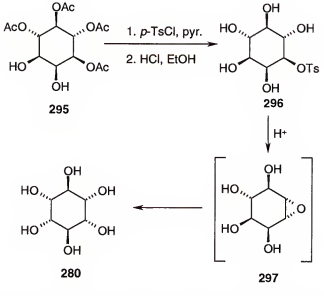


Scheme 79. The synthesis of *muco*-inositol by Dangschat and Fischer

Muco-inositol **280** was also identified as one of the products obtained by hydrogenation of hexahydroxybenzene[102] as well as by dihydroxylation of different conduritols.[103]

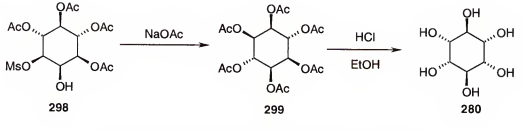
In 1966, Angyal synthesized *muco*-inositol **280** from a derivative of *myo*-inositol (Scheme 80).[104] 1,4,5,6-Tetra-*O*-acetyl-*myo*-inositol **295** was converted to tosyl derivative **296** under standard conditions, making use of an intramolecular acetyl migration. Treatment of **296** with ion-exchange resin gave anhydro derivative **297** as

an intermediate, which under the reaction conditions underwent *trans*-diaxial ring opening to furnish *muco*-inositol **280**.



Scheme 80. Angyal's first preparation of *muco*-inositol

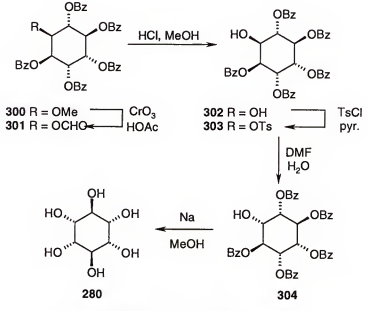
In 1967, the Lichtenthaler lab was able to prepare *muco*-inositol **280** from a *myo*-inositol derivative.[105] The methanesulfonyl ester **298** was treated with sodium acetate to give *muco*-inositol hexaacetate **299** by intermolecular rearrangement via an acetyloxonium ion. Compound **299** was then converted to *muco*-inositol **280** by acidic hydrolysis.



Scheme 81. Lichtenthaler's synthesis of *muco*-inositol

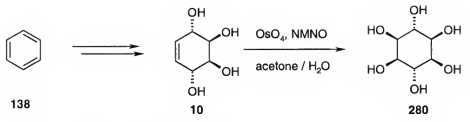
In 1972, Paulsen showed that *muco*-inositol hexaacetate was the main isomer obtained from isomerization of *myo*-inositol hexaacetate in liquid HF.[106]

In 1980, Angyal published a second synthesis, this time starting from quebrachitol derivative **300** (Scheme 82).[107] Oxidation of **300** with chromium trioxide in acetic acid converted the methyl into a formyl group, which was subsequently removed by treatment with methanolic HCl to give **302**. The hydroxyl group in **302** was tosylated, followed by hydrolysis to give 1,2,3,4,6-penta-*O*-benzoyl-*muco*-inositol **304**. Deprotection of **304** with sodium in methanol yielded *muco*-inositol **280**.



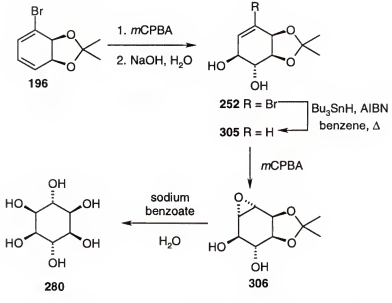
Scheme 82. Angyal's second synthesis of *muco*-inositol

Muco-inositol was also prepared by Prinzbach and co-workers during their studies of the ring openings of dianhydroinositols in 1983.[108] Carless used a chemoenzymatic approach to prepare *muco*-inositol **280** from benzene (Scheme 83).[109] Benzene was converted to conduritol A **10**. Osmylation of **10** with OsO_4 afforded *muco*-inositol **280** in 82% yield.



Scheme 83. Carless' synthesis of *muco*-inositol

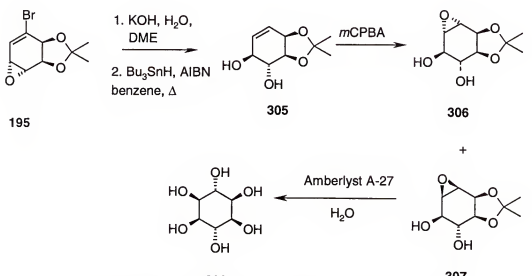
In 1993, Hudlicky reported the synthesis of *muco*-inositol **280.**[110,111] Acetonide **196** was epoxidized with *m*CPBA in 96% yield.



Scheme 84. Hudlicky's synthesis of *muco*-inositol

Ring opening under basic conditions gave diol **252,** which upon debromination under radical conditions afforded **305** in 90% over two steps. Treatment with mCPBA yielded the epoxide **306** in 71% yield. Ring opening of the epoxide along with acetonide removal in one pot yielded *muco*-inositol **280**, in 89% yield.

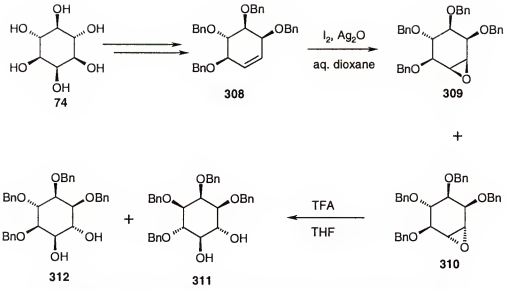
The Hudlicky group later reported a few modifications to this approach, making it more feasible for large-scale preparation.[112] Ring opening under basic conditions gave diol and debromination under radical conditions gave *trans* diol **305** in 90% yield. Epoxidation with *m*CPBA provided a mixture of α– and β- epoxides in 1:1.8 ratio in 71% yield. Hydrolysis of the epoxides **306** and **307** followed by removal of the acetonide afforded muco-inositol **280** in 89% after recrystallization.



195 **305** **306** **307** **280**

Scheme 85. Hudlicky's second synthesis of *muco*-inositol

In 1999, Chung reported their synthesis of benzylated *muco*-inositol derivative **312**, starting from *myo*-inositol **74** (Scheme 86).[113] *Myo*-inositol **74** was converted to conduritol-F derivative **308** according to a known procedure.[114] Oxidation of the double bond afforded a mixture of epoxides **309** and **310** in 86% total yield. Solvolysis of isomers under acidic conditions provided the desired *myo*-inositol **311** and *muco*-inositol **312** derivatives in yields of 14% and 64%, respectively.



Scheme 86. The synthesis of a *muco*-inositol derivative by Chung

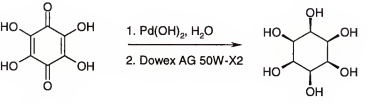
2.2.4 *Cis*-Inositol

The six hydroxyl groups of *cis*-inositol are all in *cis* arrangement to each other, and both of its two equivalent chair conformers posses three *syn*-axial hydroxyl groups. *Cis*-inositol has gained a lot of interest since it was discovered that its three axial hydroxyl groups form very strong complexes with borate ion[115,116] and several other cations.[117,118]

Cis-inositol was first prepared by Anderson and Wallis as one of the many products obtained by high-pressure hydrogenation of tetrahydroxy-*p*-quinone over a Ni-catalyst, but its configuration was not established at the time.[98] It was later fully characterized by Angyal as one of the products from the low-pressure hydrogenation over a Pd-catalyst.[119]

Angyal published the first synthesis of *cis* -inositol starting from a diacetal of *epi*-inositol to give the target molecule in eight steps.[120] Later Angyal published a

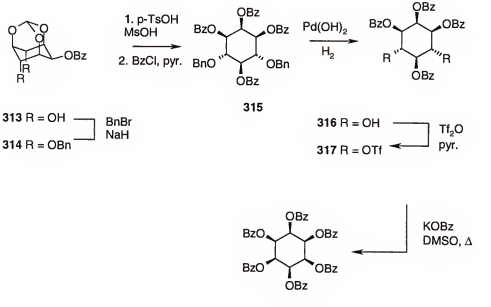
synthesis of *cis*-inositol employing catalytic hydrogenation of tetrahydroxy-*p*-quinone, followed by ion-exchange chromatography (Scheme 87).[119]



288 **281**

Scheme 87. Angyal's synthesis of *cis*-inositol

Chung synthesized *cis*-inositol hexabenzoate from a *myo*-inositol derivative.[121] *Myo*-inositol **74** was converted to 2-O-benzoyl-*myo*-inositol orthoformate **313**.



315 **316**

Scheme 87. Chung's synthesis of *cis*-inositol derivative

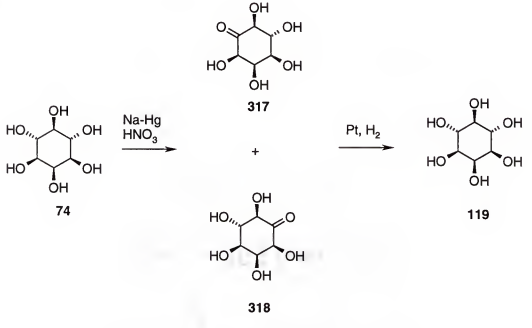
The hydroxyl groups were benzylated to afford cyclohexane derivative **314** in 82% yield. Hydrolysis of the orthofromate and subsequent benzoylation gave **315** in 91%. Hydrogenolysis of the benzyl ethers produced diol **316** in 96% yield.

Conversion of the alcohol to the triflate followed by treatment with potassium benzoate afforded *cis*-inositol hexabenzoate **375** in 32% yield.

2.2.5 *Epi*-Inositol

epi-Inositol **119** has been found to be biochemically active in reversing lithium effects on cytidine monophosphorylphosphatidate,[122] and its use as a potential antidepressant has been suggested.[123]

Posternak synthesized *epi*-inositol **119** in 1941.[124] Five years later, he proved the stereochemistry by oxidizing *myo*-inositol **74** to a mixture of two inososes, which, after hydrogenolysis gave *epi*-inositol **119** (Scheme 89).[125]

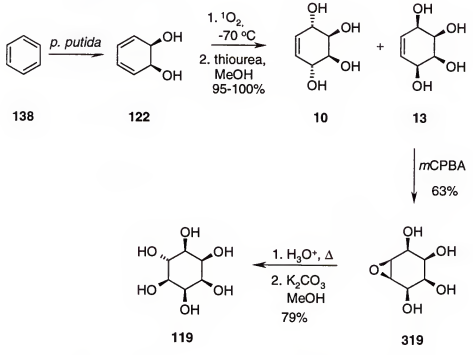


Scheme 89. Posternak's synthesis of *epi*-inositol

Epi-inositol **119** has also been prepared by hydrogenation of tetrahydroxy-*p*-benzoquinone and subsequent separation of the resulting inositol isomers,[126] as well

as by microbial oxidation of *myo*-inositol to L-*epi*-2-inosose, followed by subsequent reduction.[127]

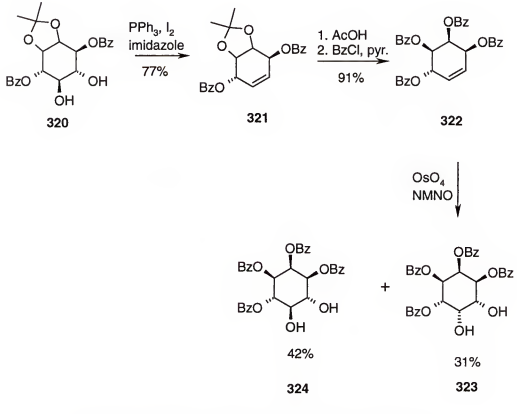
Carless *et al.* used a chemoenzymatic synthesis in their preparation of *epi*-inositol **119**.[128] Microbial oxidation of benzene **138** with *Pseudomonas putida* produced the *cis*-diol **122**. Photo-oxygenation of **122** gave a mixture of endoperoxides, which were converted by acid-catalyzed ring-opening to conduritol-A **10** and conduritol-D **14**. Conduritol-D **13** was epoxidized with peracid to give epoxide **319** in 63%. Acid-catalyzed ring-opening and ester hydrolysis under basic conditions produced *epi*-inositol **119** in 79%.



Scheme 90. Carless's synthesis of *epi*-inositol

Tschambers and coworkers synthesized *epi*-inositol as one product in a mixture of inositol stereoisomers by osmylation of *trans*-cyclohexadiene diol.[129]

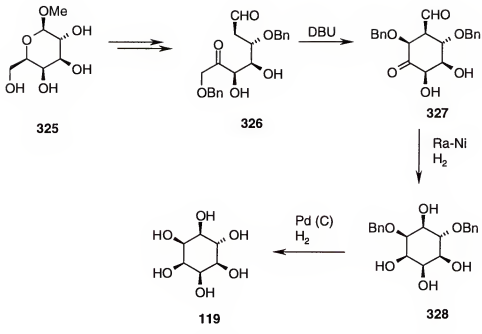
In 1999, Chung and Kwon reported their preparation of a protected derivative of *epi*-inositol (Scheme 91).[130] Diol **320** was treated with triphenylphosphine, imidazole, and iodine to give cyclohexane derivative **321** in 77% yield. Removal of the acetonide followed by benzoylation gave alkene **322** in 91% yield. Oxidation with osmium tetroxide gave a mixture of *neo*- **323** and *epi*- **324** inositol derivatives in 42% and 31% yield, respectively.



320 321 322 324 323

Scheme 91. Chung's synthesis of *epi*-inositol derivative

Corsaro and coworkers have shown that *epi*-inositol **119** can be prepared in a highly diastereoselective fashion (Scheme 92).[131] Methyl-D-galactopyranoside **325** was converted to aldehyde **326**. Treatment of **326** with DBU afforded aldol product **327** in 60% yield. This product was reduced to tetrol **328** in 92% yield. Removal of the protecting groups afforded *epi*-inositol **119**.



Scheme 92. The synthesis of epi-inositol by Corsaro.

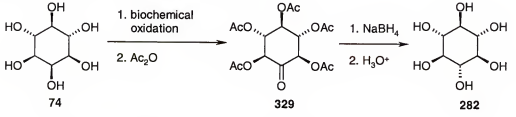
2.2.6 *Scyllo*-Inositol

Another naturally occurring inositol, *scyllo*-inositol **282**, was discovered in 1858 by Staedeler and Frerichs[132] in the organs of plagiostomous fish; they named the compound scyllitol. In 1887 an inositol was also isolated from acorns and given the name quercinitol,[133] while in 1907 Muller reported the isolation of a similar compound from the leaves of *Cocos nucifera*.[134] Later work by Muller demonstrated, that all these compounds were identical and are today referred to as *scyllo*-inositol.[135,136] *Scyllo*-inositol **282** is the all equatorial stereoisomer of *myo*-inositol **74** and has also been detected by NMR in the brain of healthy human subjects, suggesting that the *scyllo*-inositol metabolism may be regulated independently from that of *myo*-inositol **74**.[137]

The stereochemistry of *scyllo*-inositol **282** was proven by Posternak in the course of his work on the configuration of *myo*-inositol.[138,124] *Scyllo*-inositol **282** was

also obtained by Anderson and Wallis in their studies of the hydrogenation of hexahydroxybenzene.[139]

Kohne and Praefcke described an improved synthesis of *scyllo*-inositol, starting from *myo*-inositol **74**. (Scheme93).[140]



Scheme 93. The synthesis of *scyllo*-inositol by Kohne

myo-Inositol **74** was oxidized biochemically by *Acetobacter suboxydans*[141] and converted to pentaacetate **329** in 12-17% yield. Protected inososse **329** was then reduced with $NaBH_4$, followed by hydrolysis of the acetates, to give *scyllo*-inositol **382** in 69-78% yield.

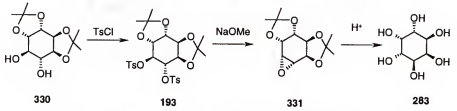
Scyllo-inositol **282** was also obtained by the Prinzbach lab in their studies towards the ring opening of dianhydro inositols.[101] More recently, *scyllo*-inositol **282** has been obtained from *myo*-inositol **74** by a reaction involving Raney-Ni and subsequent derivatization of the remaining *myo*-inositol in the reaction mixture as its orthoacetal.[142] A *scyllo*-configured inositol derivative was also obtained as a byproduct in Chung's synthesis of (±)-*chiro* inositol. [121]

2.2.7 *Neo*-Inositol

The first synthesis of *neo*-inositol **283** was reported in 1955 by Angyal and Matheson (Scheme 94).[143] Di-*O*-isopropylidene-L-*chiro*-inositol **330** was ditosylated

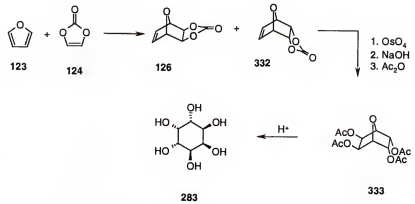
to give compound **193**, which, upon treatment with base, furnished epoxide **331**. This epoxide was hydrolyzed to *neo*-inositol **283**.

Since its discovery, the compound has also been isolated from *Croton cetidifolius*[144] and from animal tissues.[145] *Neo*-inositol **283** was later also discovered in the reaction mixture obtained by Nakajima during his hydroxylation studies of conduritols.[14]



Scheme 94. The synthesis of *neo*-inositol by Angyal

Kowarski and Sarel prepared *neo*-inositol **283** via a Diels-Alder approach, as depicted in Scheme 95.[146]

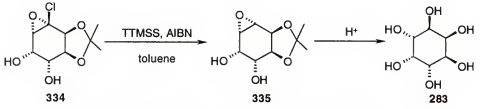


Scheme 95. The preparation of *neo*-inositol by Kowarski

Diels-Alder reaction of furan **127** with carbonate **124** gave a 3.5:1 mixture of adducts **126** and **332** in 21% total yield. Isomer **332** was then subjected to osmylation

and the resulting tetrol protected as the tetraacetate to furnish ether **333** in 9% yield. Acidic hydrolysis of **333** afforded *neo*-inositol **283** in quantitative yield.

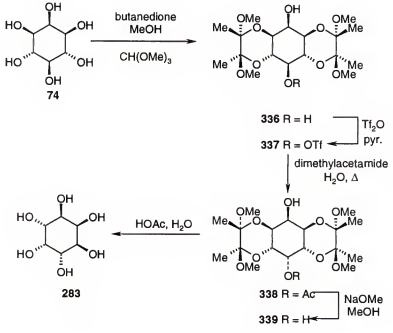
Hudlicky and coworkers published the synthesis of *neo*-inositol **283** as shown in Scheme 96.[110,111] Haloepoxide **334** was dechlorinated under radical conditions to yield epoxide **335** in 67% yield. Hydrolysis of **335** provided *neo*-inositol **283** in 50% yield.



334 **335** **283**

Scheme 96. Hudlicky's first synthesis of *neo*-inositol

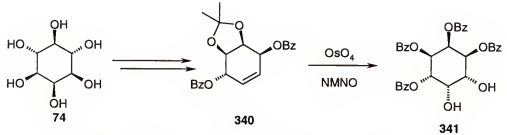
In 1998, the Potter lab published a multi-gram synthesis of *neo*-inositol **283** staring from *myo*-inositol **74** (Scheme 97).[147]



Scheme 97. Potter's synthesis of *neo*-inositol

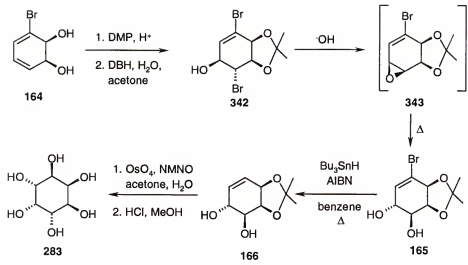
The synthesis began with a selective protection of the *trans*-diol moieties in *myo*-inositol **74** to give diol **336** in 27% yield. This was achieved by employing the *bis*-acetal protecting groups developed in the laboratories of Frost[148] and Ley.[149] One of the hydroxyl groups of **336** was converted to its triflate in 76% yield and subsequently replaced by acetate to provide alcohol **338**. Removal of all protecting groups yielded *neo*-inositol **283** in 60% yield.

Chung and Kwon prepared a *neo*-configured inositol derivative in 1999, also starting from *myo*-inositol **74** (Scheme 98).[130] *Myo*-inositol **74** was converted to cyclohexene derivative **340** according to a known procedure.[150] *Cis*-dihydroxylation afforded *neo*-inositol derivative **341** in 77% yield.



Scheme 98. The synthesis of a *neo*-inositol derivative by Chung

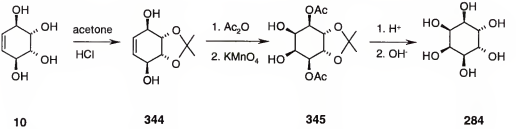
Hudlicky's group later reported a multi-gram second-generation synthesis, as shown in Scheme 99.[151] Diol **164**[152, 153] was protected as its acetonide, subsquent bromonium-ion formation and hydrolysis by water furnished bromohydrin **342**. Bromohydrin **342** was converted to the epoxide **343** under basic conditions. Upon heating of the reaction mixture, direct conversion to desired trans-diol **165** was accomplished. The debromination of halogen **165** was achieved under radical conditions. Osmylation and removal of the acetonide protecting group furnished *neo*-inositol **283** in an overall yield of 17%.



Scheme 99. Hudlicky's second-generation synthesis of *neo*-inositol

2.2.8 *Allo*-Inositol

The first synthesis of *allo*-inositol **284** was reported in 1939 by Dangschat and Fischer[10,11] (Scheme 100). Conduritol-A **10** was converted to mono-acetonide **344**, followed by acetylation of the two remaining hydroxyl groups and oxidation to give diol **345**. Removal of the protecting groups furnished *allo*-inositol **284**.

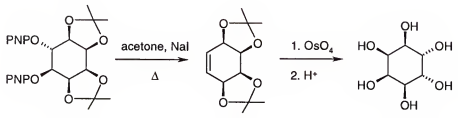


Scheme 100. The synthesis of *allo*-inositol by Dangschat and Fischer

Angyal and Gilham prepared *allo*-inositol **284** during their attempts to synthesize *cis*-inositol **281** (Scheme 101).[154] Starting from known *bis-O*-isopropylidene derivative **168**, elimination to the unsaturated derivative **169** was

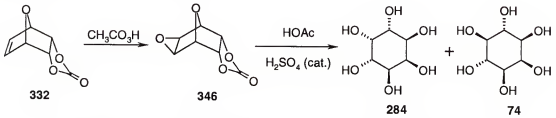
achieved by treatment with sodium iodide. Osmylation of the olefin gave *allo*-inoitol **284**.

Angyal and Gilham were hoping that the osmylation would take place from the more hindered side to give the *cis*-inositol **281**. However, they found that this was not the case and that the product they obtained was *allo*-inositol **284**, a compound that was earlier obtained in small quantities during their studies on the hydrogenation of hexahydroxybenzene.[99]



Scheme 101. The preparation of *allo*-inositol by Angyal

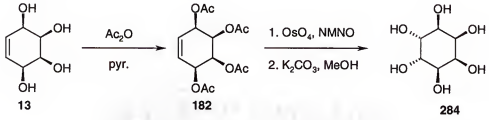
Allo-inositol **284** was also prepared by Kowarski and Sarel in a similar approach as their synthesis of *neo*-inositol (Scheme 102).[146] Diels-Alder product **332** was epoxidized using peracetic acid, followed by hydrolysis to give a mixture of *myo*-inositol **74** and *allo*-inositol **283**.



Scheme 102. The synthesis of *myo*- and *allo*-inositol by Kowarski

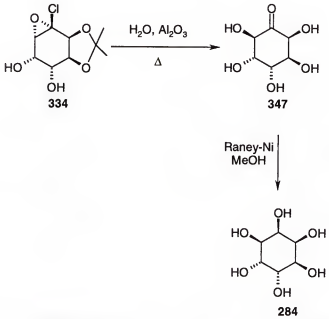
Starting from conduritol-D **13**, Carless and coworkers published their synthesis of *allo*-inositol **283** in 1992 (Scheme 103).[128] Conduritol-D **13** was

converted to its tetraacetate **182** in 79% yield. Osmylation followed by hydrolysis of the acetates afforded *allo*-inositol **283** in 60% yield.



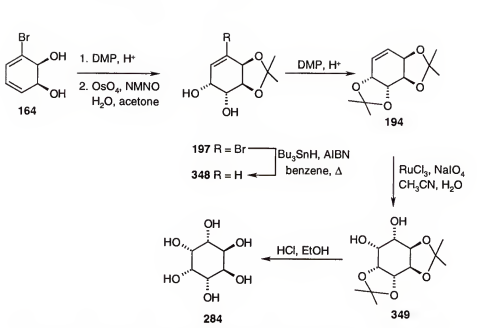
Scheme 103. Carless' synthesis of *allo*-inositol

Hudlicky and coworkers used a similar approach, incorporated in the synthesis of *neo*-inositol **283**, to synthesize *allo*-inositol **284**, employing haloepoxide **334** as starting material. (Scheme 104).[110] Haloepoxide **334** was converted to inosose **347**, which was reduced to furnish *allo*-inositol **284**.



Scheme 104. Hudlicky's first synthesis of *allo*-inositol

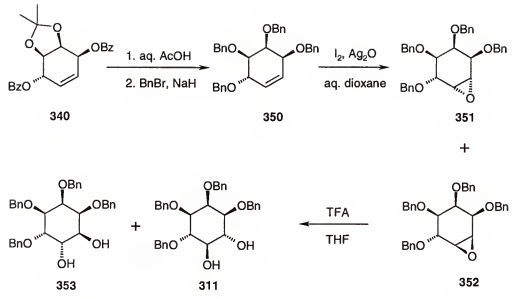
In 1997, the Hudlicky lab published a second-generation approach which allowed for the first practical multi-gram-scale synthesis of *allo*-inositol **284** (Scheme 105).[155]



Scheme 105. Hudlicky's second-generation approach to *allo*-inositol

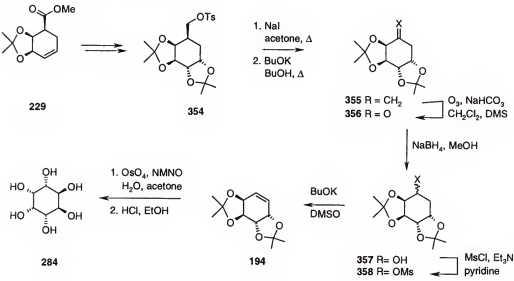
Diene diol **164** was protected as an acetonide and dihydroxylated to furnish diol **197**. Bromine removal under radical conditions occurred in 90% yield. Protection of the two free hydroxyl groups afforded cyclohexene derivative **194** in 97% yield. Ruthenium-catalyzed dihydroxylation yielded the fully oxygenated diol **349**, which was hydrolylzed to *allo*-inositol **284** in 71% yield for the two steps.

In 1999, Chung and Kwon reported the synthesis of a protected derivative of *allo*-inositol **284** (Scheme 106).[121] Cyclohexene derivative **340** was deprotected under acidic conditions, subsequent by benzylation of all four alcohols afforded **350**. Oxidation of the double bond with iodine in aqueous dioxane furnished a mixture of epoxides **351** and **352** in 89% total yield. Separation of the epoxides followed by hydrolysis of **352** under acidic conditions afforded a mixture of *allo*-inositol derivative **353** and *myo*-inositol derivative **311** in 65% and 16% yield, respectively.



Scheme 106. The synthesis of an *allo*-inositol derivative by Chung

More recently, Metha reported the synthesis of *allo*-inositol (Scheme 107).[156] Mehta started from ester **229**, which had previously been prepared by Diels-Alder reaction and Haller-Bauer cleavage.[157]



Scheme 107. Mehta's synthesis of *allo*-inositol

This compound was converted to tosyl ester **354** in a few steps. Elimination gave compound **355** in 64% yield. Ozonolysis and reduction furnished alcohol **357** in 80% yield over two steps. The alcohol was converted to mesylate **358** in 90% yield and treated with potassium tert-butoxide to afford the unsaturated derivative **194** in 75% yield. Osmylation, followed by hydroylsis of the acetonides gave *allo*-inositol **284** in 70% yield.

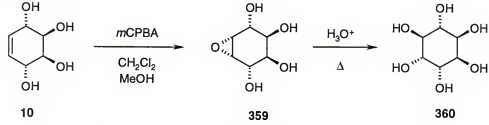
2.2.9 L-*Chiro* and D-*Chiro*-Inositol

Much interest was focused on D-*chiro*-inositol when it was found to be a putative insulin mediator. It normalizes plasma glucose in streptozotocin diabetic rats at a dose equivalent to insulin without inducing hypoglycaemia.[158]

The relative and absolute stereochemistry of L- and D-*chiro* inositol was first elucidated in 1936 by Posternak.[159] He prepared L-*chiro*-inositol from quebrachitol by demethylation and oxidatom of the product with $KMnO_4$ to mucic acid, the absolute stereochemistry of which was known. This enabled him to assign the absolute stereochemistry of the two enantiomers.

Fletcher and Findlay[160] prepared the racemic mixture of L- and D-*chiro*-inositol in 1948 and were able to show that the racemate was identical with a compound prepared earlier by Mueller in 1912.[161] This compound had been given the name *iso*-inositol by Maquenne and Tanret[162, 163] almost half a century earlier. The work of Fletcher and Findlay, as well as work by Posternak, proved that DL-*chiro* inositol was identical to *iso*-inositol. When this was realized, the name *iso*-inositol was abandoned.

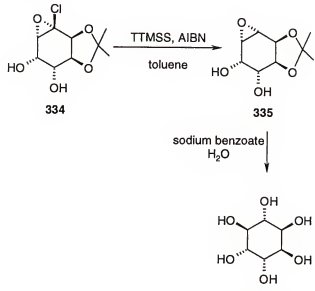
In 1992, Carless and coworkers reported a synthesis of racemic *chiro*-inositol (Scheme 108).[128] Conduritol-A **10** was oxidized with peracid to epoxide **359** in 63% yield. Ring-opening under acidic conditions produced (±)-*chiro*-inositol **360** in quantitative yield.



10 **359** **360**

Scheme 108. Carless' synthesis of (±)-*chiro*-inositol

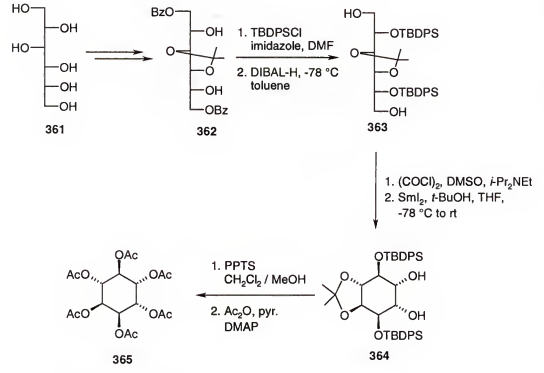
Hudlicky and coworkers reported the first total synthesis of D-*chiro* inositol **285** in 1993 (Scheme 109).[164, 110] Haloepoxide **334** was converted to epoxide **335** in 42% yield, which at elevated temperature and acid catalysis, furnished D-*chiro*-inositol **285** in 95% yield.



334 **335** **286**

Scheme 109. Hudlicky's synthesis of D-*chiro*-inositol

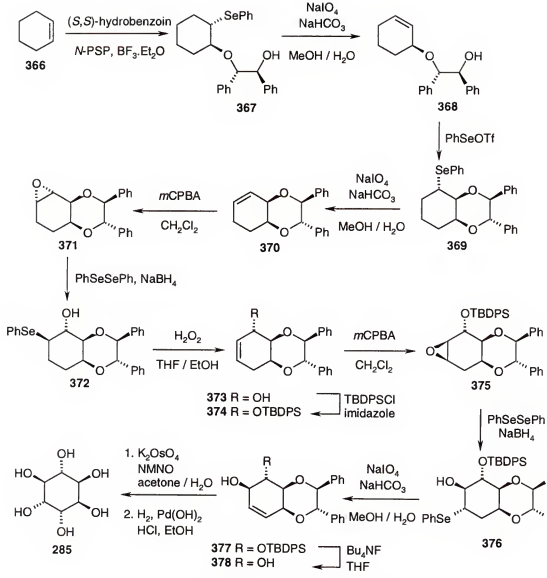
Chiara and Valle prepared L-*chiro*-inositol **286** from D-sorbitol **361** in 1995 (Scheme 110).[165]



Scheme 110. The synthesis of L-*chiro*-inositol hexaacetate by Chiara

D-Sorbitol **361** was selectively protected using a known procedure[166] for the corresponding D-mannitol derivative to furnish **362** in 15% overall yield. Silylation of the hydroxyl groups in **362** were achieved in 70% yield. Debenzoylation gave diol **363** in 80% yield. Using a procedure developed in their lab, a one-pot sequence of Swern oxidation and SmI_2-promoted intramolecular pinacol coupling[167] gave the L-*chiro* configured derivative **364** in 78% yield. Compound **364** was then deprotected to give L-*chiro*-inositol **286**, which was characterized as its hexaacetate **365**.

Kim and coworkers reported an approach to D-*chiro*-inositol **285** in 1998 (Scheme 111).[168]

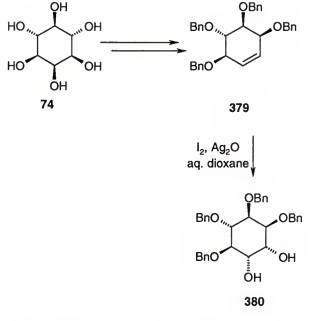


Scheme 111. The synthesis of D-*chiro*-inositol by Kim.

Cyclohexene **366** was treated with *N*-(phenylseleno)-phthalimide (*N*-PSP),(*S*,*S*)-hydrobenzoin and BF_3Et_2O to furnish chiral oxyselenide **367** (40%), which was transformed into olefin **368** in 92% yield. Intramolecular oxyselenylation of **368** gave bicyclic dioxane **369** (68%), which provided **370** after elimination in 90% yield. Treatment of **370** with *m*CPBA gave epoxide **371** (60%), which was opened with a selenium nucleophile to provide **372** in 95% yield. Elimination afforded allylic

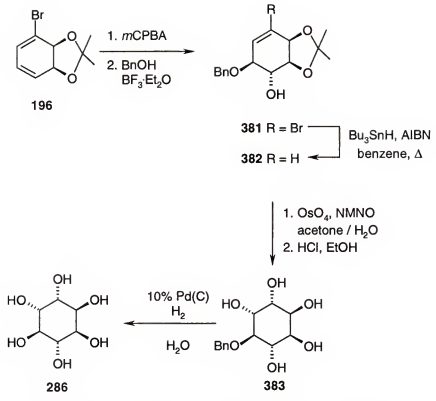
alcohol **373** in 96% yield. After protection of the alcohol , the remaining double bond was epoxidized in 51% yield and opened with PhSeNa again in 83% yield. Elimination gave **377** in 90% yield. After removal of the silyl-protecting group, the molecule was dihydroxylated in 87% yield and all protecting groups were removed to give D-*chiro*-inositol **285** in 71% yield.

Chung prepared a (±)-*chiro*-inositol derivative from *myo*-inositol **380** (Scheme 112).[121] *Myo*-inositol **74** was converted to conduritol-F derivative **379** by a known procedure.[114] Hydroxylation with OsO_4/ NMNO afforded (±)-*chiro*-inositol derivative **380** in 95% yield.



Scheme 112. The preparation of a (±)-*chiro*-inositol derivative by Chung

Hudlicky and coworkers recently reported the synthesis of L-*chiro*-inositol **286** (Scheme 113),[112] using a similar approach to that utilized in their synthesis of *muco*-inositol **280**.

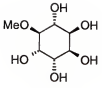


Scheme 113. Hudlicky's synthesis of L-*chiro*-inositol

Acetonide **196** was converted to an epoxide, which was subsequently opened with benzyl alcohol under Lewis-acid conditions to furnish **381**. The bromine was removed under radical conditions. Compound **382** was then dihydroxylated and the acetonide hydrolyzed with hydrochloric acid in ethanol to give **383**. The final step consisted of hydrogenolysis of the benzyl ether to produce L-*chiro*-inositol **286** in quantitative yield.

2.2.10 Pinitols

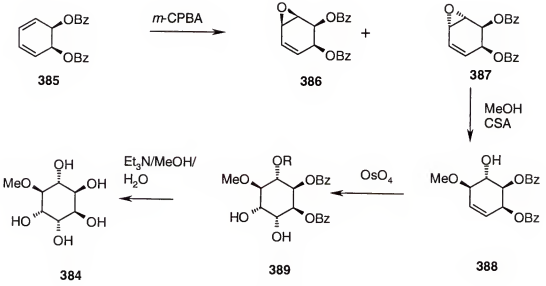
Pinitol **384** was discovered by Berthelot[169] in the exudates of *Pinus lambertiana* Dougl. (sugar pine). It has also been isolated from the heartwood of five other *Haploxylon* pines (soft or white pines)[170] and from *Sequoia sempervirens* (redwood).



384

Pinitol **384** has been shown to be a feeding stimulant for the larvae of the yellow butterfly *Eurema hecabe mandarina*[171] and inhibits larval growth of Heliothis zea on soybeans.[172,173] Recently it has been shown to have hypoglycemic and antidiabetic activity in normal and alloxan-induced diabetic albino mice.[174]

In 1955, Angyal and Matheson reported the first synthesis of pinitol **384**.[143] In 1987, Ley reported the synthesis of (±)-pinitol **384** via microbial oxidation of benzene.

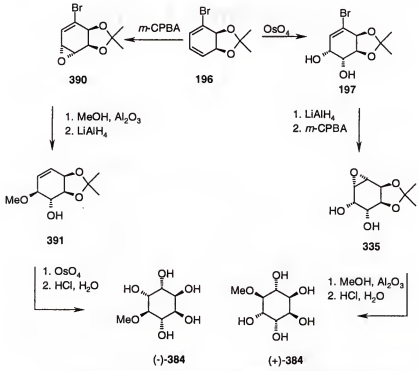


Scheme 114. Ley's synthesis of pinitol

Benzene was transformed to *cis*-1,2-dihydroxycyclohexane-3,5-diene via *Pseudomonas putida*.[175] *Cis*-1,2-dihydroxycyclohexane-3,5-diene was benzylated with benzoyl chloride to give **385**. Compond **385** was epoxidized with mCPBA to

give epoxides **386** and **387**. Epoxide **387** was treated with methanol and camphorsulfonic acid to give methylated compound **388**. Osymlation of **388** gave diol **389** which upon hydroylsis afforded (±)-pinitol **384**. Later Ley and Sternfeld were able to resolve the enantiomers with menthoxyacetyl chloride yielding optically pure (+)-and (-)-pintol **384**.[176]

In 1990 Hudlicky and coworkers reported an endantiodivergent synthesis of both enantiomers of pinitol **384**.[177]



Scheme 115. Hudlicky's synthesis of pinitols antipodes

Cis-1,2-dihydroxycyclohexane-3,5-diene **196** was epoxidized with *m*CPBA to give epoxide **390**. Epoxide **390** was treated with methanol and Al_2O_3 and subsequently reduced with $LiAlH_4$ to give alcohol **391**. Alcohol **391** was osmylated and hydrolyzed to (-)-pinitol **384**.

Cis-1,2-dihydroxycyclohexane-3,5-diene **196** was osmylated to give diol **197**. Diol **197** was reduced with $LiAlH_4$ and then epoxidized with *m*CPBA to give epoxide **335.** Epoxide **335** was methylated with methanol and Al_2O_3 and hydrolyzed to (+)-pinitol **384**.

2.3 Cyclitols

In 1994, Billington and co-workers reported a useful tool for studying the cyclitol modulation of insulin secretion *in vitro*.[26] Billington showed that conduritols were able to modulate insulin secretion from isolated pancreatic islets in the present of glucose (Table 1).

Table 1. Conduritol Insulin modulation

Conduritol	% Change at 2.8mM	% Change at 16.7mM
Conduritol-A **10**	+45	-30
Conduritol-B **11**	+41	+50
Conduritol-C **12**	+27	-20
Conduritol-D **13**	0	0
Conduritol-E **14**	+12	+15
Conduritol-F **15**	+9	-3

Given the interesting effects of conduritol-A **10** and -B **11**, Billington prepared a series of analogs having fused ring analogs in place of the conduritol double bond (Figure 6). These analogs were chosen based on the hypothesis that four hydroxyl groups of conduritol-A **10** in the a,b,b,a stereochemistry were responsible for the

biological activity, with the double bond acting as a conformational restraint. This hypothesis is based on the saturated analog of conduritol-A **10** being less active.

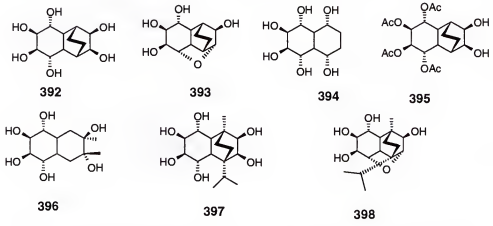


Figure 6.Examples of insulin-release modulators prepared by Billington

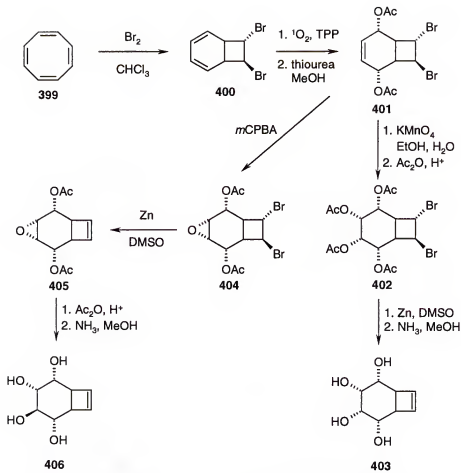
The conduritols showed a range of effects. Conduritol A **10**, B **11**, and C **12** at low glucose levels and B **11** at high glucose levels showed a stimulatory effect. Conduritol-A **10** and C **12** at high glucose levels had an inhibitory effect.

In contrast, the bicyclic analogs are almost all inhibitors of insulin secretion at all glucose concentrations.

Table 2. Cyclitol Insulin Modulation

Compound	% Change at 2.8mM	% Change at 16.7mM
392	-18	+44
395	-60	-23
393	0	-70
396	-60	0
394	-45	-35
397	-30	-30
398	-60	-45

In 1994, the Balci group reported *bis*-homo-conduritol-D and F as potentially biologically active conduritol derivatives (Scheme 116).[68,178,]

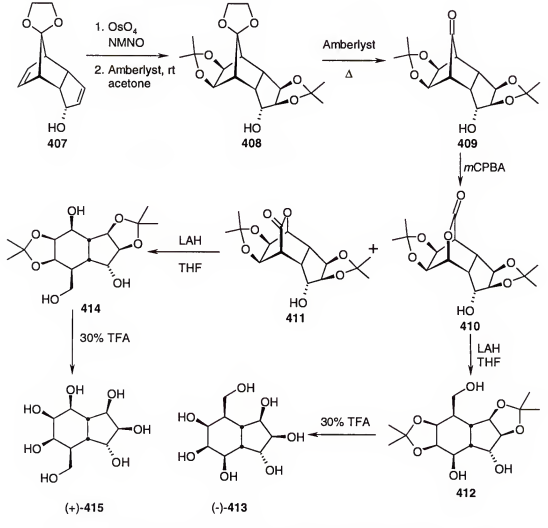


Scheme 116. The synthesis of *bis*-homo-conduritols by Balci .

Bromination of cyclooctatetraene **399** gave bicyclic compound **400**. Photooxygenation of **400** with singlet oxygen followed by reduction with thiourea afforded alkene **401** in 60% yield. Alkene **401** afforded a pathway to the *bis*-homo-conduritol-D and F derivatives. For the synthesis of the conduritol-D derivative, the double bond was oxidized with potassium permanganate and the resulting alcohols protected as acetates to give all-*cis* tetraacetate **462** in 68% yield. Debromination with zinc followed by hydrolysis of the esters under basic conditions afforded *bis*-homo-conduritol-D **403**.

For the synthesis of the conduritol-F derivative, alkene **401** was epoxidized and bromine was eliminated with zinc in DMSO to give alkene **405** in 84% yield. Acetolysis of the epoxide followed by removal of the acetates under basic conditions produced *bis*-homo-conduritol-F **406** in 90% yield.

In 1999, Mehta and Reddy synthesized polyhydroxylated hydrindanes as potential glycomimetics (Scheme 117).[179]

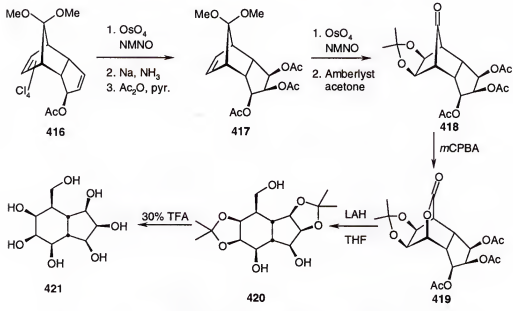


Scheme 117. The synthesis of polyhydroxylated hydrindanes by Mehta.

Alcohol **407** was obtained in enantiopure form by kinetic enzymatic acylation.[180] Osmylation of the two double bonds followed by protection of the

resulting diols afforded alcohol **408** in 50% yield. The acetal was removed with ion-exchange resin to give ketone **409** in 92% yield. The ketone was subjected to Bayer-Villiger oxidation to afford a 60:40 mixture of the two esters, **410** and **411**, respectively. Both isomers were reduced with LAH to afford triols **412** and **414** in 70% yield. Hydrolysis afforded the free polyhydroxylated hydrindanes **413** and **415** in 95% yield.

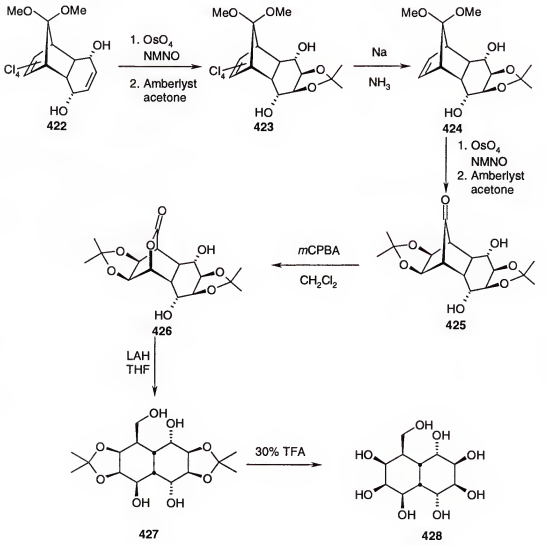
Mehta and Reddy also prepared the all-*cis* analog of **421** (Scheme 118). Allyl acetate **416** was converted to triacetate **417** in three steps in 41% overall yield.



Scheme 118. Mehta's synthesis of an all-*cis* polyhydroxy hydrindane

Hydroxylation of the double bond followed by protection of the resulting diol gave **418** in 88% yield. Bayer-Villiger oxidation furnished ester **419** in 95% yield. Reduction of the esters followed by hydrolysis of the acetonides produced the all-*cis* polyhydroxy hydrinane **421** in 60% yield. All three compounds were found to be inactive for glycosidase inhibition.

Later, Mehta and coworkers reported the synthesis of several decalin-based polyols (Scheme 119).[181]

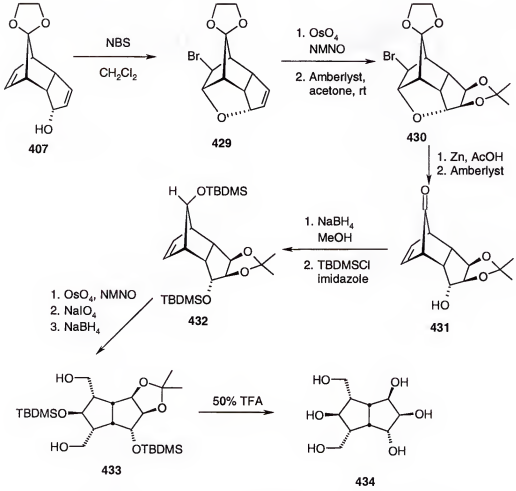


Scheme 119. Mehta's synthesis of a polyhydroxy decalin

Diels-Alder product **422**[182] was osmylated followed by protection of the resulting diol to afford **423** in 58% yield. Dehalogenation of **423** under dissolving metal conditions produced alkene **424** in 88% yield. Another osmylation reaction followed by protection of the resulting diol and hydrolysis of the dimethyl acetal gave diol **425** in 92% yield. Bayer-Villiger oxidation of the latter resulted in the formation

of lactone **426** in 42%. Reduction of the esters followed by hydrolysis of the acetals afforded polyol **428** in 54% yield.

Mehta and coworkers also reported the preparation of diquinane-based polyols (Scheme 120).



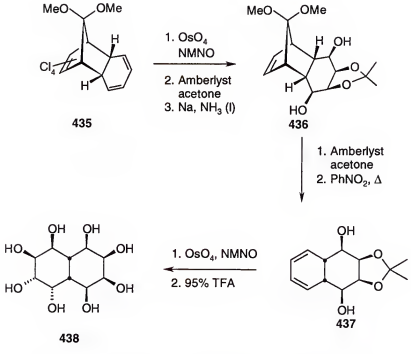
Scheme 120. Mehta's synthesis of a diquinane based polyol

Tricyclic alcohol **407** was converted to bromoether **429** by treatment with NBS in 80% yield. Osmylation of the double bond, followed by protection of the resulting diol as an acetonide, furnished **430** in 75% yield. Reductive cleavage of the bromoether followed by hydrolysis of the acetal gave enone **431** in 75% yield.

Reduction of **431** gave **432** in 90% yield after protection of the alcohol as a TBDMS-ether. Compound **432** was then subjected to osmylation, periodate cleavage, and reduction to afford **433** in 60% yield. Hydrolysis of the protecting groups under acidic conditions produced polyol **434** in 90% yield.

Polyols **428** and **434** were screened for their inhibition activity against α- and β- galactosidase and β-mannosidase, but no significant inhibition was found.

In 1999, Mehta and Ramesh also reported the synthesis of decalin-based bicyclitols (Scheme 121).[183]

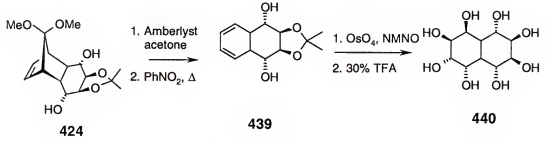


Scheme 122. The synthesis of a bicyclitol by Mehta

Diene **435**[184] was subjected to osmylation and the resulting diol protected as an acetonide. Reductive dehalogenation afforded diol **436** in 24% yield. Cleavage of the dimethyl acetal followed by thermally induced decarbonylation led to diene **437** in 61%. Double osmylation and deprotection under acidic conditions provided bicyclitol

438 in 81% yield. Compound **438** was found to be a powerful inhibitor of α-glucosidase with a K_i value of 12 μM.

Mehta and Ramesh also reported the synthesis of a second bicyclitol with different stereochemistry (Scheme 123). Removal of the acetal group of diol **424** with ion-exchange resin, followed by decarbonylation at elevated temperatures, afforded diene **439** in 32% yield. Double osmylation of the double bonds and acidic hydrolysis of the acetals furnished bicyclitol **440** in 66% yield. Compound **440** exhibited no inhibition towards α- or β-glycosidases, indicating that the stereochemical pattern of the hydroxyl groups in these bicyclitols has major influence on the inhibition properties, since **438** was found to be very active.

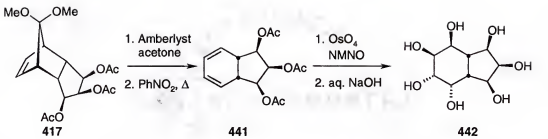


424 **439** **440**

Scheme 123. Mehta's synthesis of a bicyclitol

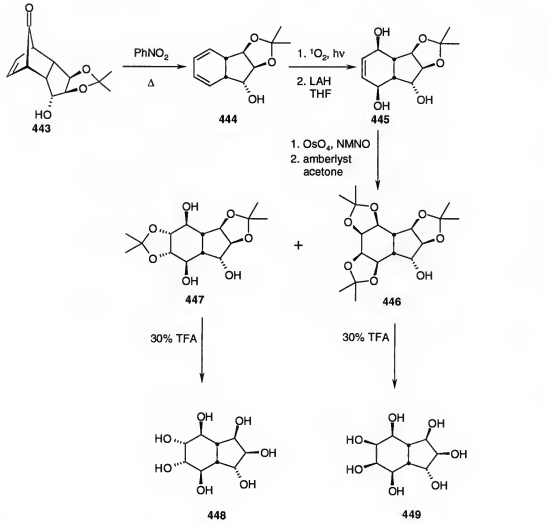
Recently, Mehta and Ramesh reported the synthesis of additional racemic hydrinane-based polycyclitols (Scheme 124).[185]

Alkene **417** was treated with ion-exchange resin to accomplish hydrolysis of the dimethyl acetal and then subjected to thermal decarbonylation to give diene **441** in 44% yield. Double osmylation followed by hydrolysis of the acetates under basic conditions provided polyol **442** in 53% yield.



Scheme 124. Mehta's synthesis of a bicyclitol

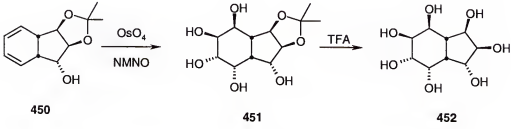
Mehta and Ramesh also reported two different bicyclitol diastereomers (Scheme 125).



Scheme 125. Mehta's synthesis of new bicyclitols

Alcohol **443** was subjected to thermal decarbonylation to give diene **444** in 67% yield. Singlet-oxygen addition followed by reductive cleavage of the peroxide bond afforded triol **445** in 48% yield. Osymlation of **445** gave two diastereomers, which were separable after protection to give **446** and **447** in yields of 56% and 17%, respectively. Both isomers were deprotected with trifluoroacetic acid to provide polyols **448** and **449** in yields of 88% and 92%, respectively.

Starting from alcohol **450,** Mehta were also able to prepare another isomer with different stereochemistry (Scheme 126). Alcohol **450** was subjected to double osmylation to give **451** in 83% yield. Acidic hydrolysis of the acetal protecting groups provided polyol **452** (89%).



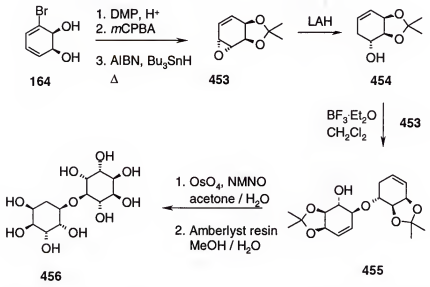
Scheme 126. Mehta's synthesis of bicyclitol

All new bicyclitols were evaluated for their inhibition properties toward glycosidases and found to be inactive except for **442**, which proved to be a moderate inhibitor of α-glucosidase with a K_i of 84 μM.

2.4 Cyclitol Oligomers

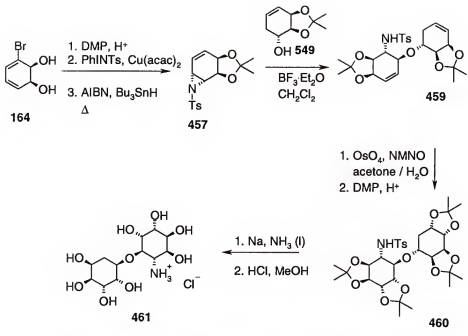
In 1994 Hudlicky and Thorpe reported the first synthesis of a cyclitol dimer (Scheme 127).[186] *Cis*-Bromodiol **164** was protected as its acetonide and epoxidation with peracid, followed by radical debromination gave epoxide **453**.[152, 153] Ring

opening with LAH furnished secondary alcohol **454**.[111] The coupling of the epoxide **453** with alcohol **454** under Lewis-acid catalysis produced dimer **455** in 75% yield. Osmylation of the double bonds in 74% yield followed by deprotection under acidic conditions furnished L-*chiro*-inositol-*gala*-quercitol **456** in 98% yield.



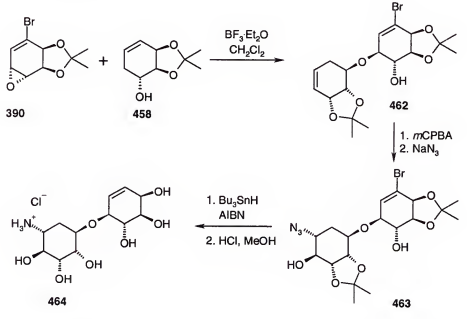
Scheme 127. The synthesis of L-*chiro*-inositol-*gala*-quercitol by Hudlicky

In 1996, Hudlicky and co-workers reported the synthesis of a variety of 1,2-L-*chiro*-inositol conjugates and oligomers(Scheme 128).[187, 188]By using a strategy similiar to that previously described in Scheme 127, Hudlicky et al. were able to prepare amino-inositol conjugate **461**. Diol **164** was converted to vinyl aziridine **457** in three steps. Compound **457** was coupled with alcohol **458** to furnish dimer **459** in 52% yield. The latter was osmylated and the resulting diols protected as acetonides to give **460** in 69% yield. Deprotection of the amine followed by acidic hydrolysis of the acetonides furnished dimer **461** in 92% yield.



Scheme 128. Hudlicky's synthesis of amino-inositol-dimer

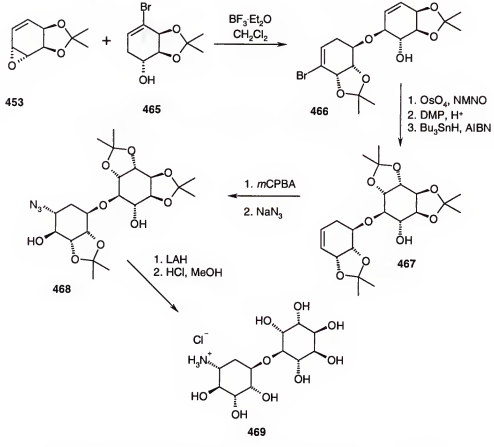
Conduritol-amino-inositol dimer **464** was prepared as outlined in Scheme 129. Epoxide **390** and alcohol **458** were coupled under Lewis-acid conditions to furnish dimer **462** in 64% yield.



Scheme 129. Hudlicky's synthesis of a conduritol-amino-inositol conjugate

Epoxidation followed by ring opening with sodium azide gave azidohydrin **463** in 87% yield. The latter was subjected to tributyltin hydride reduction to remove the bromide and to reduce the azide to an amine in 79% yield. Acidic hydrolysis yielded conduritol-amino-inositol conjugate **464** in quantitative yield.

Hudlicky also prepared a more fully hydroxylated analog **469** as depicted in Scheme 130.

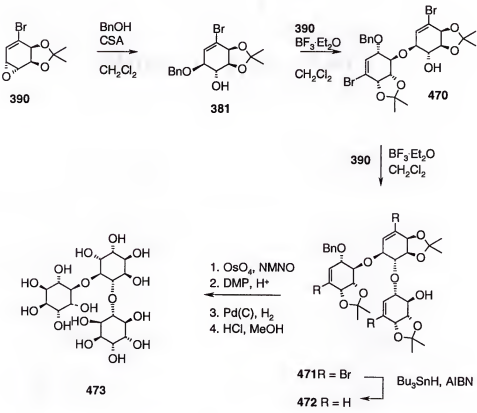


Scheme 130. Hudlicky's synthesis of amino-inositol conjugate

Vinyl epoxide **453** was reacted with alcohol **465** to give dimer **466** in 61% yield. The dimer was double osymalated in 72% yield and the resulting diols protected as acetonides followed by reductive cleavage of the halogen to yield alcohol **467** in 89% yield. The double bond in **467** was transformed to its epoxide (86%)

subsequent ring opening with sodium azide gave **468** in 82% yield. Reduction of the azide with LAH and subsequent acidic hydrolysis produced dimer **469** in 68% yield.

Hudlicky's group also prepared several L-*chiro*-inositol oligomers (Scheme 131).

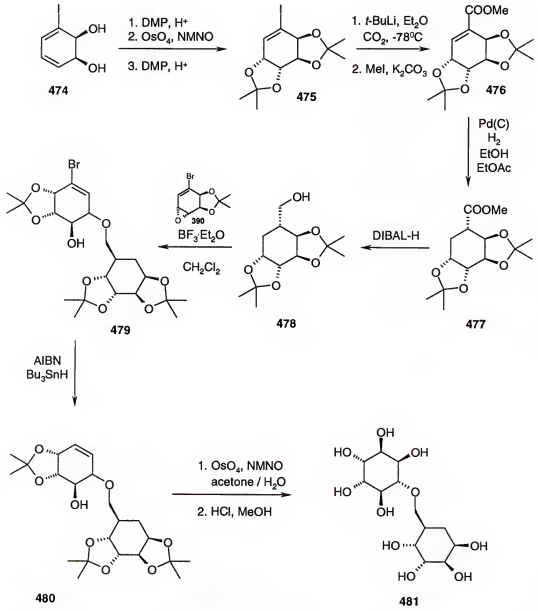


Scheme 131. Hudlicky's synthesis of a L-*chiro*-inositol trimer

Vinyl epoxide **390** was reacted with benzyl alcohol via camphorsulfonic acid catalysis to afford alcohol **381** in 55% yield. Alcohol **381** was reacted with vinyl epoxide **390** to produce dimer **470** in 79% yield. This dimer was once again reacted with **390** to furnish trimer **471** in 55% yield. The bromides in **471** were then removed under radical conditions to afford **472** in 81% yield. The three double bonds in compound **472** were hydroxylated and the resulting diols protected as acetonides.

Hydrogenolysis of the benzyl group and cleavage of the acetals under acidic conditions yielded L-*chiro*-inositol trimer **473** in 53% yield.

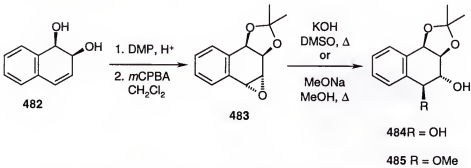
Hudlicky also reported the synthesis of an *O*-linked pseudosugar conjugate (Scheme 132).



Scheme 132. Hudlicky's synthesis of an *O*-linked pseudosugar conjugate

Diol **474** was converted to its acetonide followed by osmylation and subsequent protection to give alkene **475** in 75% overall yield. Methoxycarbonylation of the latter afforded ester **476** in 90% yield. Hydrogenation of the double bond yielded ester **477** (92%), which was reduced to produce primary alcohol **478** in 74% yield. The latter was reacted with vinyl epoxide **390** under Lewis-acid conditions to yield coupled product **479** in 62%. Removal of the bromide under radical conditions afforded alkene **480** in 91% yield. Hydroxylation of the double bond followed by acidic hydrolysis of the acetals gave the free pseudosugar conjugate **481** in 87% yield.

In 1997, the Hudlicky group reported the first synthesis of polyhydroxylated tetrahydronaphthalene ethers (Scheme 133).[189]

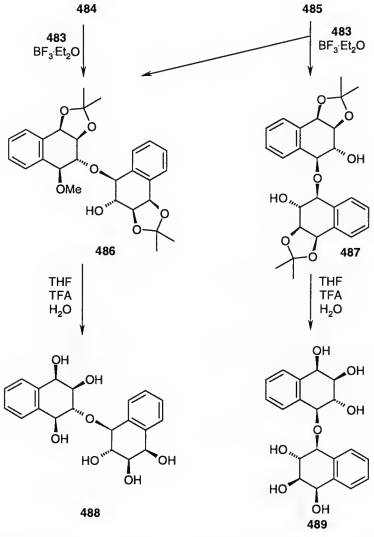


Scheme 133. Hudlicky's synthesis of tetrahydronaphthalene alcohols

Dihydronapthtalene diol **482** was protected as its acetonide, the epoxidozed to afford **483**. Ring opening with either KOH in DMSO or NaOMe in MeOH gave diol **484** and alcohol **485**, respectively.

Using Lewis acid catalysts, the coupling reaction was achieved either by reacting either **484** with epoxide **483** to give dimer **486**, or by reacting **485** with epoxide **483** to give a 3:1 mixture of **486** and **487** (50% total yield) that was easily

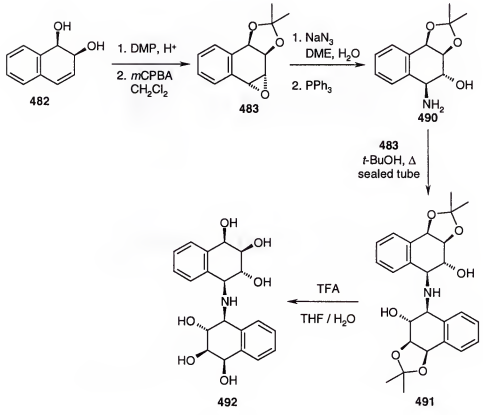
sseparated. Both dimers could be deprotected under acidic conditions in 80% yield to afford tetrahydronaphthalene dimers **584** and **585**.



Scheme 134. Hudlicky's synthesis of polyhydroxylated tetrahydronaphthalene dimers

The Hudlicky group also reported the synthesis of an amino-bridged tetrahydro-naphthalene dimer (Scheme 135).[190] Diol **482** was converted to epoxide **483** under standard conditions. Ring opening of **483** with sodium azide, followed by reduction of the amine under Staudinger conditions[191, 192] afforded amine **490**. The latter was reacted with epoxide **483** in *t*-BuOH at elevated temperature to produce *N*-

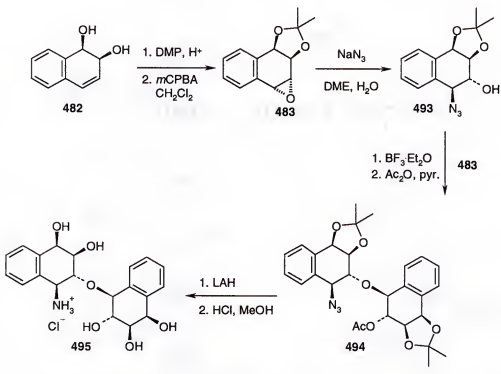
linked dimer **491** in 50% yield. Compound **491** was deprotected under acidic conditions to yield free *N*-linked tetrahydronaphthalene dimer **492** in 90% yield.



Scheme 135. Hudlicky's synthesis of an amino-bridged tetrahydronaphthalene dimer

In 1999, the Hudlicky group reported the synthesis of an aminohydroxylated tetrahydronaphthalene dimer (Scheme 136).[193] Diol **482** was converted in two steps into epoxide **483**. Epoxide **483** was opened with sodium azide to provide azidohydrin **493**. Lewis-acid catalyzed ring opening of **483** with **493** followed by protection afforded dimer **494** in 27% yield. Reduction of the azide and the ester followed by deprotection with hydrochloric acid in methanol provided dimer **495** as its hydrochloride salt. All dimers were also evaluated for their inhibitory activity toward

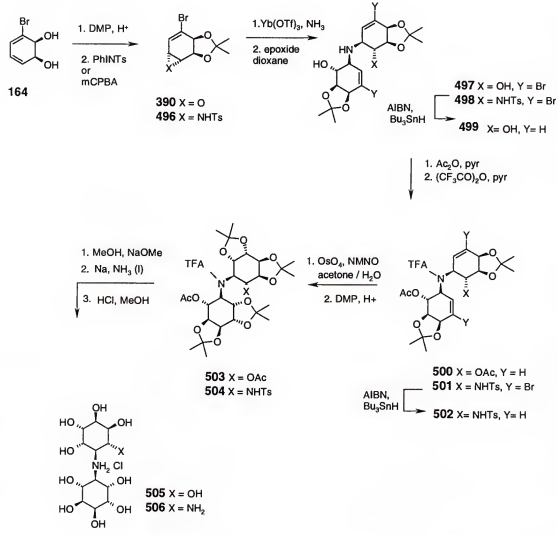
glycosidases, but none of the compounds showed any inhibition at concentrations up to 10 mM.



Scheme 136. Hudlicky's synthesis of an aminohydroxylated tetrahydronaphthalene dimer

In 2001, the Hudlicky group reported a new class of unnatural saccharide mimics. Novel O- and N-linked inositol oligomers were synthesized using a chemo-enzymatic approach (Scheme 137). Bromocyclohexadiene-*cis*-diol was converted to either the vinyl epoxide or N-tosyl vinyl aziridine in two steps. Conduramine oligomers **497** and **498** were obtained by a one-pot procedure in which vinyl epoxide **390** or vinyl aziridine **496** were treated with ammonia. The resulting amino alcohol or trans-diamine was subsequently reacted with vinyl epoxide **390** to produce **495** and **497** in yields of 94% and 79%, respectively. Dehalogenation of **497** with tributyl tin hydride (TBTH) afforded **499** in 83% yield. The hydroxyl groups were treated with

acetyl anhydride to give the acetates in 89% yield. The conversion of the secondary amine to trifluoroacetamide **500** (98%) yield which was dehalogenated with TBTH in 73% yield.



164

390 X = O
496 X = NHTs

497 X = OH, Y = Br
498 X = NHTs, Y = Br
499 X= OH, Y= H

500 X = OAc, Y = H
501 X = NHTs, Y = Br
502 X= NHTs, Y= H

503 X = OAc
504 X = NHTs

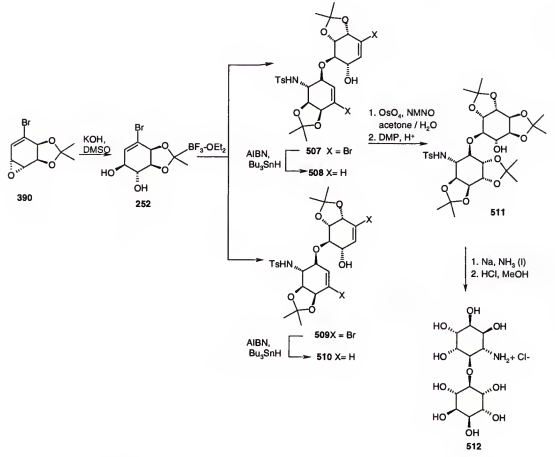
505 X = OH
506 X = NH_2

Scheme 137. O- and N-linked Inositol oligomers

Osmylation of the double bonds in **500** afforded the *cis*-diols which were protected as the acetonides to give **503** in 53% yield. A similar reaction sequence provided dimer **504** starting from **502** in 61% yield. Basic hydrolysis of the acetate and the trifluoroacetamide, followed by removal of the acetonides with MeOH-HCl

provided the hydrochloride salt **505** in 87% yield. The acetate and trifluoroacetamide in **504** were removed under basic conditions in 57% yield, and the sulfonamide was removed with sodium in liquid ammonia in 84% yield. Acidic hydrolysis gave **506** in 77% yield.

The O-linked inositol oligomer was obtained via a convergent approach (Scheme 138). The ring opening of vinyl epoxide **340** with KOH afforded *trans*-diol **252** in 63% yield.



Scheme 138. O-linked inositol oligomer using a convergent approach

Trans-diol **252** was reacted with vinyl aziridine **496** to yield **507** and **508** in 52% yield. Vinyl bromide **507** was debrominated under radical conditions to give **508**

in 68% yield. The latter was dihydroxylated and its *cis*-diols protected as acetonides to give **511** in 60% yield. This procedure was repeated for **509** to give **511.** The tosyl amine was deprotected with Na/NH_3. Deprotection of the acetals under acidic conditions gave **512** in 52% yield

2.5 Electrochemical Reduction

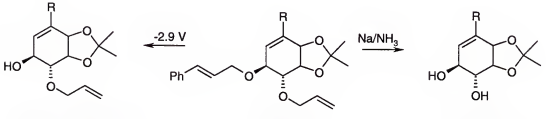
Electrochemisty provides a wide variety of chemical conversions using relatively simple and inexpensive equipment with advantages of speed, yields, and simplicity of workup. Electrochemistry can also lead to more efficient or reagent-free reactions. Hudlicky defines overall efficiency as effective mass yield (EMY).[194] This is further defined as the percentage of the mass of desired product relative to the mass of all non-benign material used in its synthesis. Using electrochemical methods, EMY can be maximized since nonhazardous materials would be used.[194]

Through the years, attempts have been made to apply electrochemical methods as a means of deprotection.[195] Such methods offer the possibility that groups may be removed sequentially merely by varying the electrolysis potential.

The protection of the alcohol functionality by means of simple and readily available allyl protecting groups has frequently been used in organic synthesis.[196] The cleavage of allyl ethers to their parent alcohols by chemical methods may involve isomerization to enol ethers with $(Ph_3P)_3RhCl$[197] or KOtBu/ DMSO[198] followed by acid hydrolysis. Reactions utilizing Pd/C, SeO_2/HOAc or Lewis acids have also been reported.

When sensitive polyfunctional molecules are involved, cleaving allyl ether groups under non-hydrolytic conditions are desirable. Electrochemical reactions may be used for the removal of protecting groups[199] but these reactions require high potentials. The use of catalysts[200] facilitated electron transfer processes and increased the use of electrochemical methods in protection chemistry.

Recently, the Hudlicky group reported that the cleavage of a cinnamyl system can be selectively controlled in the presence of a multiple allylic system (Scheme 139).[201] Hudlicky was able to show selectivity in the removal of cinnamyl groups over allyl groups using mild conditions. The most complex system contained endocyclic and exocyclic cinnamyl groups as well as an endocyclic and exocyclic allyl groups. Only the exocyclic groups were cleaved electrochemically.



515 R=H 78% yield
516 R= Ph 83% yield

513 R=H
514 R= Ph

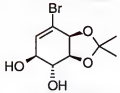
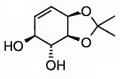
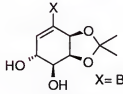
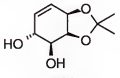
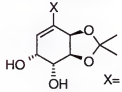
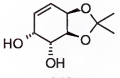
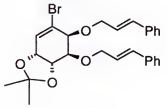
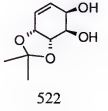
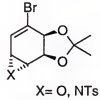
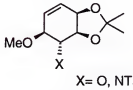
517 R=H
518 R= Ph

Scheme 139. Selectively cleavage in a multiple allylic system

In 1999, Hudlicky reported the use of electrochemistry as an alternative to tin reagents for the reduction of vinyl halides in several inositol synthons[202](Table 3).

Vinyl halides were subjected to electrochemical reduction conditions. The lack of reactivity of allylic alcohols or allylic ethers at the applied potentials allowed for selective reduction. Electrochemical methods provide for selective reduction of vinyl iodides over vinyl bromides, with better yields than analogous tin methodology.

Table 3. Electrochemical Reduction

Entry	Starting material	Applied Potential	Product	Yield
1	 252	-3.2V	 305	62%
2	 519	-3.0V	 166	X=Br 59% X=Cl no reaction
3	 520	-3.0V	 348	X=Br 57% X=I 50%
4	 521	-3.2 V	 522	54%
5	 390, 496	-2.4 V	 523	X=O 54% X=NTs 50%
6	524	-2.2 V	164	73%

In 2003, Hudlicky studied electrochemical deprotection of the cinnamyl group from ethers, esters, and carbamates.[203] The focus of this study was the selective

deprotection of the cinnamyl group attached to oxygen and nitrogen as well as over allyl or benzyl systems. It was shown that both the cinnamyl and cinnamyloxycarbonyl can be selectively removed in the presence of an allyl or alkoxycarbonyl group. It was also shown that the cinnamyl group could be removed in the presence of a benzyl ether. This study also indicated that oxygen deprotection occurs selectively over nitrogen except in the case of a carbonate/carbamate system.

The next chapter of this dissertation will discuss the chemo-enzymatic electrochemical synthesis of cyclitol oligomers. This approach uses a synthetic pathway that is unlike any of the preceding syntheses. Using a "green" approach towards these oligomers, the synthetic route entails an efficient, environmentally friendly pathway to cyclitols.

Various types of cyclitols have been presented in the previous section. The following discussion will address the syntheses, structural attributes, and biological activities of conduritol-F and *muco*-inositol oligomers.

CHAPTER 3
DISCUSSION

3.1 Introduction

The review of the literature presented in the preceding section has shown that cyclitols have interesting properties. Much of the focus in the area has been on developing new methods of glycosidation[204] and chemo-enzymatic syntheses of carbohydrates.[205] Little has been published in coupling these monomeric units. Recently, Hudlicky synthesized inositol oligomers setting the stage for a new class of unnatural inositol analogs that resemble disaccharides in their three-dimensional hydrogen bonded tertiary structure and molecular volume.[206]

With this background, we set out to prepare novel oligomers based on the *muco*-inositol or conduritol-F configuration and study their structure and biological properties. The structures of these synthetic targets are depicted in Figure 4.

525 **526**

muco-Inositol series conduritol F series

Figure 4.

The potential benefits of these compounds can be indicated by molecular modeling of tetramers in which the three-dimensional shape can be programmed by using monomers of different configurations.

This discussion has been divided into three sections. The first section describes the synthesis of the oligomers including electrochemical procedures for the selective reduction of vinyl bromide and cinnamyl ether. The second section describes the biological evaluation as glycosidase inhibitors. The third section describes the molecular modeling of the oligomers.

3.1.1 Synthesis of conduritol-F oligomers

Our initial goal was the synthesis of conduritol-F **15** and its oligomers. It was envisioned that using the microbial oxidation of bromobenzene **528** to yield the homochiral *cis*-diol **164** would provide the *cis*-diol functionality required in our target compound. The key step was the selective manipulation of one of the olefin functionalites while keeping the other olefin intact. We envisioned incorporation of the *trans*-substituted functionality via epoxide opening under nucleophilic conditions. A retro synthetic scheme is shown is Figure 5.

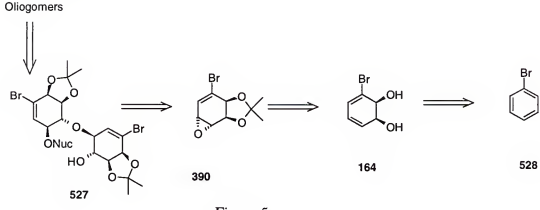
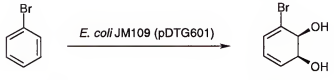


Figure 5.

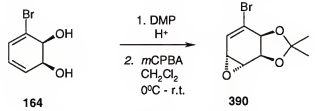
Homo-chiral diol **164** is easily available by whole-cell fermentation of bromobenzene **528** with *E.coli* JM109 (pDTG601) as depicted in Scheme 140.



528 **164**

Scheme 140. The whole-cell fermentation of bromobenzene

This reaction was performed on a 10 L scale and furnished the desired chiral diol **164** in >10 g/L yield. Diol **164** was then converted to vinyl epoxide **390** (Scheme 141).



164 **390**

Scheme 141. Formation of epoxide

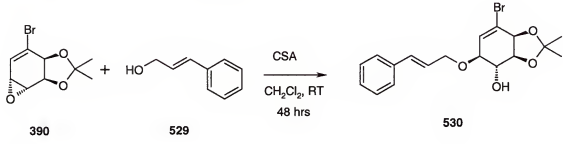
Protection of diol **164** as an acetonide, which was subsequently subjected to epoxidation, afforded vinyl epoxide **390** in 70% yield for two steps.

The choice of the nucleophile is very important in this synthetic scheme. We envisioned using the nucleophile as a protecting group. The nucleophilic opening of the epoxide provided the expected diaxial product. The preferred attack was at the allylic position. Under acidic or Lewis acid conditions, the protonation or chelation of the epoxide oxygen weakens the C-O bond and increases the positive charge on the carbon atom which is stabilized by the olefin. This group would block the allylic hydroxyl, freeing the adjacent hydroxyl for further coupling. Also if a protecting group is used as a

nucleophile, it could reduce the number of synthetic step which would be equally beneficial.

Earlier, Hudlicky showed that the cinnamyl group and halogens can be electrochemically reduced with yields comparable to radical reductions.[202] This would combine two otherwise troublesome reactions into one simple "reagent-free" reaction.

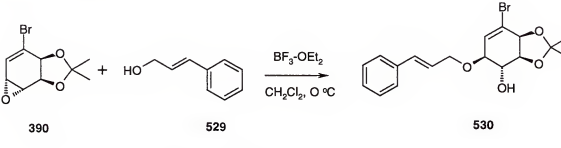
In our first attempt to prepare this intermediate, it was envisioned to introduce the cinnamyl group through nucleophilic attack of the epoxide **390** (Scheme 142). This reaction proceeded sluggishly without going to completion.



390 **529** **530**

Scheme 142. Synthesis of cinnamyl-ether

This reaction was optimized using another Lewis acid, BF_3-OEt_2. Using 5 molar equivalents of the nucleophile **529**, the reaction was completed in 30 minutes in 73% yield (Scheme 143).

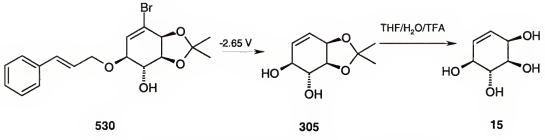


390 **529** **530**

Scheme 143. Synthesis of cinnamyl-ether

For the synthesis of conduritol-F **15**, the cinnamyl ether **530** was subjected to electrochemical reduction conditions. In one synthetic step, debromination and cinnamyl

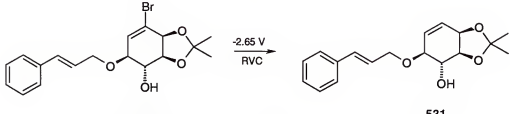
cleavage were achieved in 53% yield. Conduritol-F **15** was obtained quantitively upon treatment with acid (Scheme 144).



530 **305** **15**

Scheme 144. Electrochemical synthesis of conduritol-F

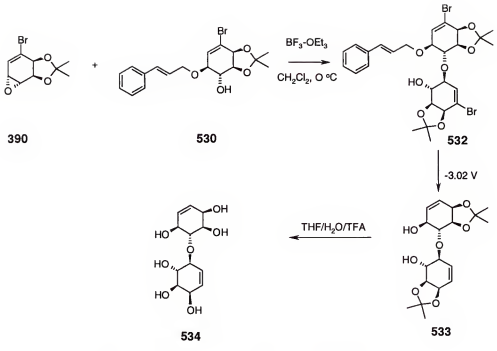
With the ability to reduce the halogen and the cinnamyl group in one step, our attention turned to selective dehalogenation in the presence of the cinnamyl group. From previous research, we reported that compounds containing both cinnamyl ether and vinyl bromide moieties afforded products with both cinnamyl group removal and debromination upon electrolysis. Noting that the cinnamyl group is removed at a slower rate using a carbon electrode,[207] we sought to selectively remove the bromide in the presence of cinnamyl ether. Thus, electrolysis of **530** at -2.65 V with a reticulated vitreous carbon (RVC) electrode provided **305** in 66% yield (Scheme 145).



530 **531**

Scheme 145. Selective debromination

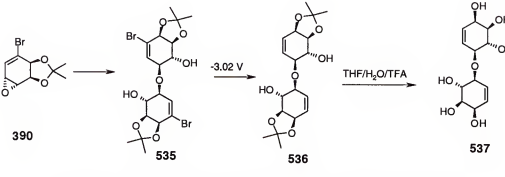
In the higher conduritol oligomers, cinnamyl ether **530** was reacted with vinyl epoxide **390** to yield the protected dimer **532** in 40% yield.



Scheme 146. Synthesis of conduritol-F dimer

Electrolysis of **532** at -3.02 V gave dimer **533** in 40%. Dimer **533** was treated with a THF/H_2O/TFA (4:1:1) to yield conduritol F dimer **534** in 93% yield (Scheme 146).

An alternative conduritol-F dimer was also synthesized (Scheme 147). The C-2 symmetrical dimer **535**[208] was subjected to electrolysis conditions to afford diene **536** in 60 % yield. Diene **536** was subjected to acidic hydrolysis to afford conduritol-F dimer **537** in 95% yield.



Scheme 147. Synthesis of C-2 symmetrical conduritol-F dimer

3.1.2 Synthesis of muco-Inositol oligomers

For the synthesis of the *muco*-inositol series, we envisioned starting with the homochiral *cis*-diol in order to incorporate one of the *cis*-diol units needed in the desired target (Figure 6). The introduction of the *trans*-diol could be accomplished by di-epoxidation followed by hydrolysis. Since opening of the epoxide would result in a *trans*-diol configuration, we planned to achieve this coupling by a series of epoxide openings.

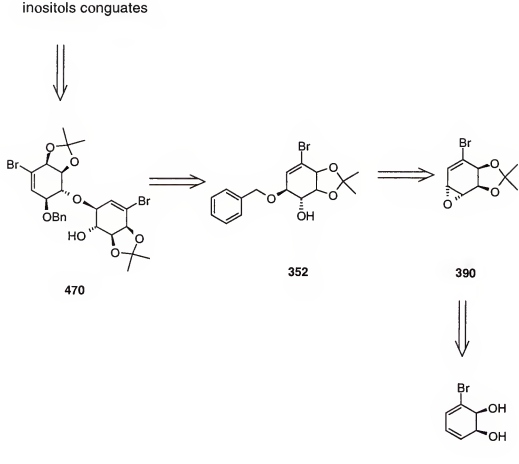
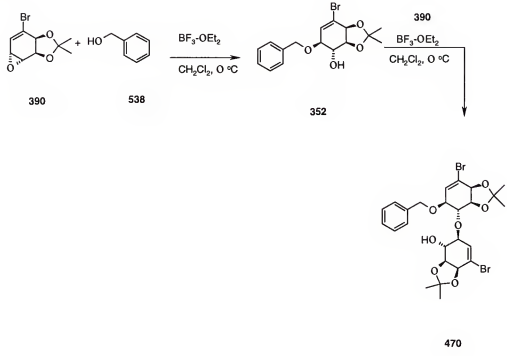


Figure 6. Retrosynthetic analysis for targets in the of *muco*-inositol series

Epoxide **390** was subjected to ring opening conditions involving benzyl alcohol **538** and BF_3-OEt_2 to give the benzyl ether **352** in 75% yield.(Scheme 148) Reaction of epoxide **390** with benzyl ether **352** under Lewis-acid catalysis afford alcohol **470** in 55% yield.

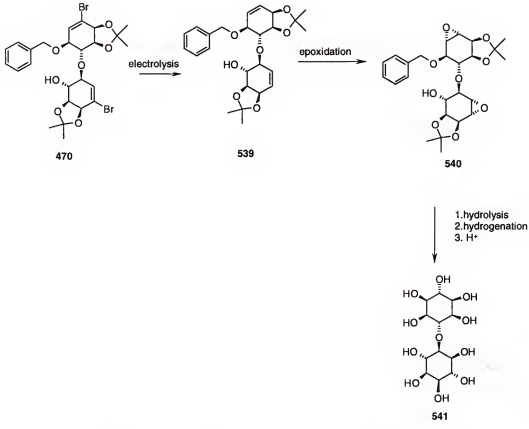


Scheme 148. Synthesis of benzylated dimer

The key step in the synthesis of the inositol series is the introduction of the *trans*-diol configuration to provide the desired stereochemistry of *muco*-inositol. This involved halogen removal and olefin oxidation.

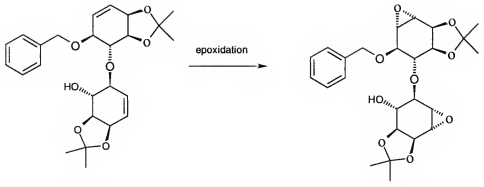
The halogens were removed electrochemically using a procedure implemented in our laboratory.[202] The dibromide **470** was subjected to electrolysis conditions to afford the diene dimer **539** in 77% yield. With the diene in hand, epoxidation of the olefin follow

by hydrogenation and hydrolysis would afford the *muco*-inositol dimer **541** (Scheme 149).



Scheme 149. Synthetic pathway to *muco*-inositol dimer

Epoxidation of the diene proved to be problematic. At this stage, several different reactions conditions were investigated (Table 4).



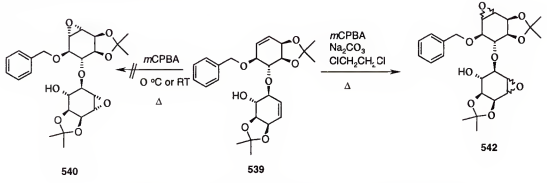
539 **540**

Table 4. Studies on epoxidation

Entry	Reagent	Solvent/ Temperature	Results
1	*m*CPBA	CH_2Cl_2 / R.T.	Decompostion
2	*m*CPBA	CH_2Cl_2 / O °C	Decomposition
4	*m*CPBA	$ClCH_2CH_2Cl$ / reflux	Decomposition
5	*m*CPBA Na_2CO_3	$ClCH_2CH_2Cl$/ reflux	18% yield mixture of epoxides
6	CF_3CO_3H Na_2CO_3	CH_2Cl_2 / R.T.	Loss of acetonides
7	DBH NaOH	Acetone/ H_2O	Low yield
8	$VO(acac)_2$	Benzene	No product recovered
9	trifluoroacetone oxone	MeCN/H_2O O °C	40% mixture of epoxides
10	Acetone oxone		Low yield

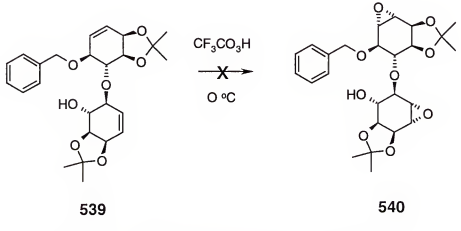
In our efforts toward the synthesis of the dimer **541**, we tried similar conditions to achieve to the synthesis of epoxide **390.** The first attempt to epoxidize the diene involved the use of *m*CPBA. Diene **539** was treated with *m*CPBA in CH_2Cl_2 at room temperature for 18 h. This led to a complex product mixture in addition to starting

material. The reaction was repeated at lower temperatures, but also failed to produce product. This reaction was repeated at higher temperatures and afforded no product. Using sodium carbonate as a pH buffer gave epoxide **540** in 18% yield as a mixture of α- and β- epoxides (Scheme 150).



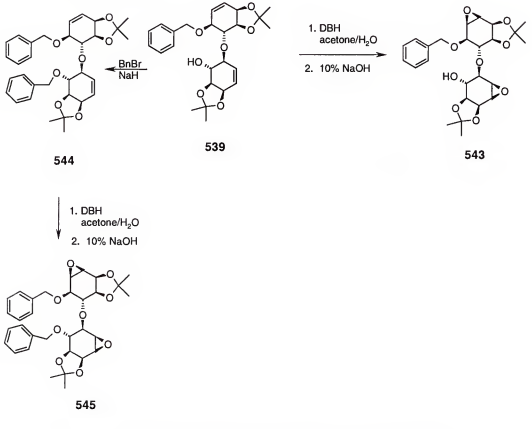
Scheme 150. *m*CPBA approach to *muco*-inositol dimer

A second peroxyacid was used in an effort to achieve epoxidation (Scheme 151). Peroxytrifluoroacetic acid, synthesized *in situ,* was reacted with diene **539**. This resulted in removal of the acetonides in additon to production of trace amounts of deprotected product.



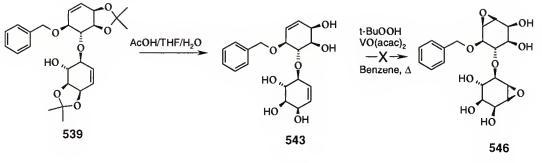
Scheme 151. Peracid approach to *muco*-inositol dimer

An alternative pathway to making the epoxide is via the bromohydrin (Scheme 152). Hudlicky has shown that the *syn*-epoxide can be opened in such a way that it leads to a convergent pathway to the *muco*-inositol configuration.[209] Diene dimer **539** was treated with 1,3-dibromo-5,5-dimethyl hydantoin (DBH) in an acetone/water mixture (5:1) to give the bromohydrin which was sequently treated with 10% NaOH to give the *syn*-epoxide **543** in trace amounts. In an effort to improve the yield, the free hydroxyl of diene **539** was treatment with benzyl bromide to give benzylated diene **544** in 75% yield. Diene **544** was then treated with DBH and subsequently treated with NaOH to give epoxide **545** in 30% yield.



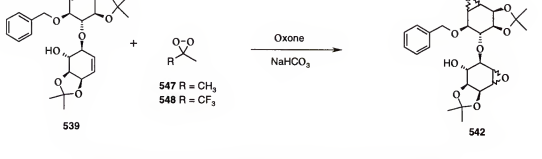
Scheme 152. Bromohydrin approach to *muco*-inositol dimer

Another attempt to make the syn-epoxide using Sharpless and Michealson's conditions[210] (t-BuOOH/VO(acac)$_2$ was invoked. Diene **539** was treated with a (2:1:1) mixture of acetic acid, THF, and H_2O at 65 °C to yield pentol **543** in quantitative yield. Pentol **546** was treated with T-BuOOH and VO(acac)$_2$ in benzene at reflux. This reaction led to a complex mixture of products (Scheme 153).



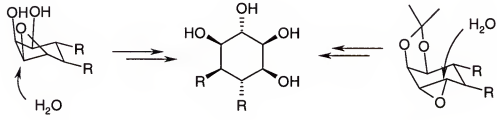
Scheme 153. *Syn*-epoxide via peracid approach to *muco*-inositol dimer

An approach to epoxidation of diene **539** using dioxirane was also performed (Scheme 154). The first attempt used acetone as a precursor to the *in situ* generated dimethyl dioxirane **547**. A second attempt to make the di-epoxide **540** via dioxirane involved the use of trifluoroacetone as a precursor for the *in situ* generation of methyl(trifluoromethyl) dioxirane **548**.[211] Di-epoxide **542** was obtained in 40% yield as a mixture of the α–and β– epoxides.



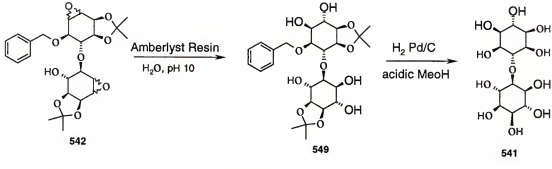
Scheme 154. Dioxirane approach to *muco*-inositol dimer

Our laboratories have shown that either α– or β– epoxides lead to a convergent product.[209] This pathway is based on the trans-diaxial opening of either substrate which provides the same *trans*-diol configured intermediate (Scheme 155).



Scheme 155. Diaxial opening of α– or β– epoxides

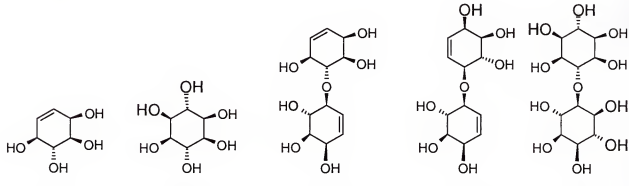
With the epoxide **542** in hand, a *trans*-diaxial opening of both epoxides was attempted with hopes of obtaining the convergent intermediate. The di-epoxide **542** was stirred in water at reflux in the presence of strongly basic Amberlyst resin for 6 days. This afforded *trans*-diol **549** in 61% yield. *Trans*-diol **549** was treated with palladium on activated carbon under a hydrogen atmosphere in acidic methanol to afford *muco*-inositol dimer **541** in 97% (Scheme 156).



Scheme 156. Diaxial opening of α– or β– epoxides to muco-inositol dimer

With the *muco*-inositol and conduritol-F oligomers in hand (Figure 7),their biological activitywas investigated. These compounds possess numberous hydroxyl

groups that resemble the three-dimensional features found in the natural sugars. The dimers lack the glycosidic bond that normally allows transformation by hydrolytic enzymes.



15 **280** **533** **537** **541**

Figure 7. Synthesized Oligomers

3.2 Glycosidase Inhibition

Inositol and conduritol dimers have interesting properties that lead us to investigate their potential as glycosidase inhibitors. All inositol dimers possess an extended series of hydroxyl groups, which resemble the three-dimensional features found in the natural sugars. Since all inositol dimers lack the glycosidic bond, they cannot be processed by a hydrolytic enzyme.

To evaluate their potential as glycosidase inhibitors, all compounds were screened against different hydrolases. The assay[206] used allowed a facile evaluation of all compounds screened against the corresponding enzymes at or close to their optimum pH value, and the liberated *p*-nitrophenolate was monitored at 400 nm without a basic quench. A multicell spectrometer, which allowed the monitoring of the enzymatic reaction at different inhibitor concentrations over a period of time, was used. For active

compounds, a decrease of the initial rate with increasing inhibitor concentration is expected Plotting the reaction rates against the inhibitor concentrations gives inhibition curves from which the IC_{50} values can be obtained.

Before testing the individual dimers, we performed the assay using a standard with known literature values.[212] Known inhibitor 1,4-diamino-1,4-dideoxy-D-mannitol was used with a substrate concentration of 2.5 μM and a pH value of 6.0. An IC_{50} of 0.35 μM was obtained (Figure 8). This correlated to the literature value of 0.5 μM, which was recorded at a pH of 4.5 and a substrate concentration of 0.33 mM.

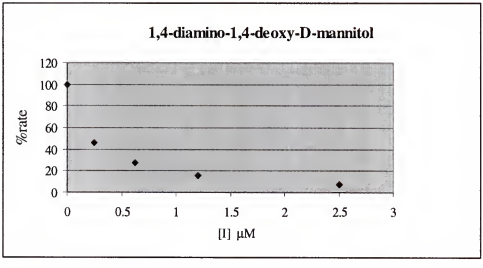


Figure 8. Inhibition of α-mannosidase by DIM

The results of the inhibtion studies are shown in Figures 9-13. The graphical representation in Figure 9 shows that conduritol-F **15** was shown to be a decent inhibitor of α-galactosidase with a IC_{50} of approximately 600 μM. The inhibitor was not active against the remaining five enyzmes. Muco-inositol **280** was shown to be virtually inactive (Figure 10). It showed very weak inhibitory activity against α-galactosidase.

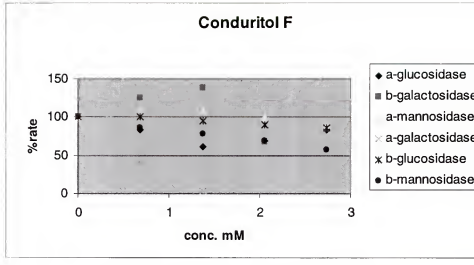


Figure 9. Inhibition results of Conduritol F

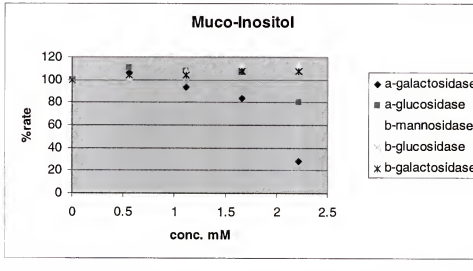


Figure 10. Inhibition results of *muco*-inositol

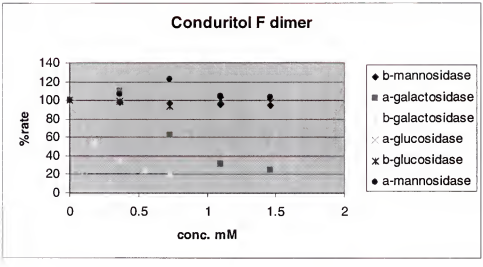


Figure11. Inhibition results of Conduritol F Dimer

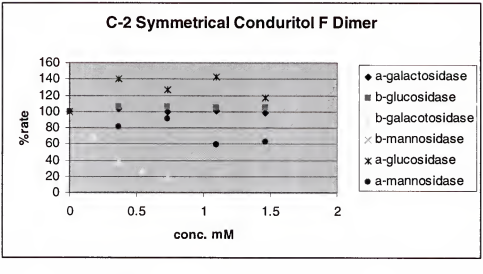


Figure12. Inhibition results of C-2 Symmetrical Conduritol F Dimer

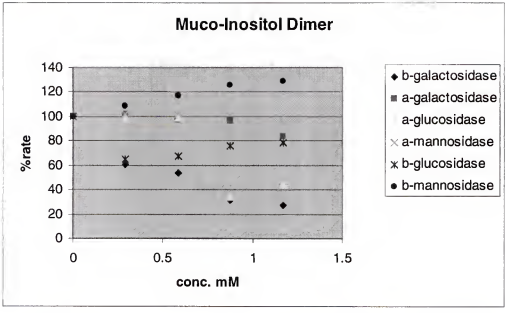


Figure13. Inhibition results of Muco-inositol Dimer

Conduritol F dimer **533** proved to be a strong inhibitor of α-glucosidase with an IC_{50} of aproximately 60 μM. It was also a moderate inhibitor of both β-galalactosidase and α-galalactosidase with $IC_{50's}$ of aproximately 250 μM and α- 750 μM respectively (Figure 11).

Symmetrical Conduritol F dimer **537** was proven to be a moderate inhibitor of β-galalactosidase with an IC_{50} of approximately 250 μM and a weak inhibitor of β-mannoosidase with an IC_{50} of aproximately 1.5 mM. There was no detectable inhibiton against the other glycosidases (Figure 12).

Muco-inositol dimer **541** was shown to be a modest inhibitor of β-galactosidase with an IC_{50} of approximately 600 μM (Figure 13). Dimer **541** also showed weak inhibitor activity of α-glucosidase with an IC_{50} of 800 μM.

Table 5. Inhibition summary

Compound	α-glucosidase	β-glucosidase	α-galactcoside	β-galactocosidase	α-mannosidase	β-mannosidase
Conduritol-F **15**	N.A	N.A	N.A	600 μM	N.A	N.A
muco-Inositol **280**	N.A	N.A	N.A	N.A	N.A	N.A
Conduritol-F dimer **533**	60 μM	N.A	850 μM	190 μM	N.A	N.A
Symmetrical Conduriol-F dimer **537**	N.A	N.A	275 μM	250 μM	N.A	1.50 mM
muco Inositol Dimer **541**	800 μM	N.A	N.A	600 μM	N.A	N.A

N.A. = less than 50% inhibition at an inhibitor conc. of 2000 μM

All compounds (except for *muco*-inositol dimer **280**) showed moderate to strong inhibition of β-galactosidase (Table 5). The conduritol-F dimers proved to be stronger inhibitors in comparsion to the monomers and muco-inositol. Hudlicky and coworkers have previously shown that nitrogen-linked inositol performed with similar results.[206]

These compounds were active gainst β-galactosidase. The reason for this remains unclear since the hydroxylation pattern of the conduritol and inositol dimers do not match the one of β-galactosides or the galactosyl cation. The stereochemical arrangement of the hydroxyl groups present in this molecule does not match that of D-galactose. This leads to the speculation that hydroxyl groups from both conduritol and inositol units might participate in the binding to the active site of the corresponding enzyme.

3.3 Molecular Modeling

Using the Spartan SGI software available from Wavefunction, Inc., molecular modeling was conducted to obtain a three-dimensional picture of the oligomers. All

results were calculated by using Monte-Carlo simulation to find the minimum energy conformations. These structures were further optimized by semi-empirical (AM1) methods. All calculations were performed with parameters for gas phase medium.

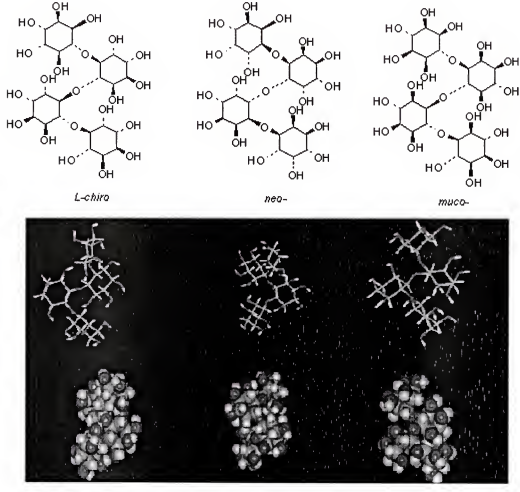


Figure 14. Three-Dimensional Models of Inositol Tetramers

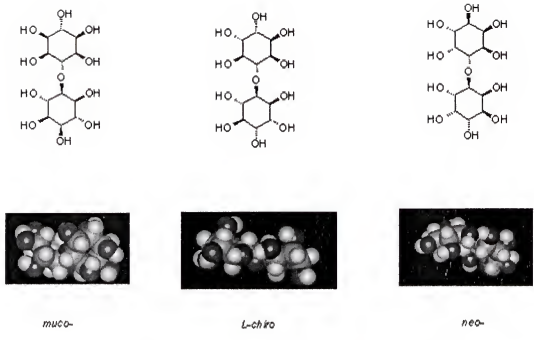


Figure 15. Three-Dimensional Models of Inositol Dimers

Just as in the L-*chiro*- and *neo*- inositols series, *muco*-inositol dimer's individual monomers appear to position themselves approximately ninety degrees from one another in order to avoid steric interactions between α-substituents.

The structural arrangement of higher order oligomers of L-*chiro*, *neo*-, and *muco*-inositols were also calculated and quite a noticeable conformational difference in the three inositols was observed. *Neo*-inositol tetramers and octomers tend to form loops while L-*chiro*- and *muco*-inositol oligomers preferentially form helices as shown in the figure below:

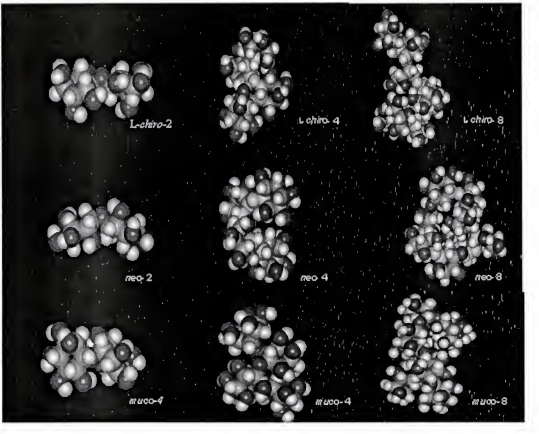


Figure 16. Three-Dimensional Models of Inositol Tetramers

CHAPTER 4
CONCLUSION

Using a whole-cell fermentation of bromobenzene with *E. coli* JM109 (pDTG601), a chemoenzymatic synthesis of several novel inositol and conduritol oligomers were reported. The fermentation produced homo-chiral *cis*-diol as a common intermediate that led to all the novel cyclitols.

In the synthesis of conduritol oligomers, a selective electrochemical reduction of vinyl bromide in the presence of cinammyl ether was achieved. The importance of this reaction is that it is environmentally benign and the yields are comparable to those of tributyl tin hydride.

The synthesis of the *muco*-inositol oligomers involved a convergent approach. The key step in the sequence pathway involved the synthesis of the α– or β– epoxides that were opened to a single product. These *muco*-inositol oligomers have been found to show interesting intramolecular hydrogen-bonding properties, similar to that of L-*chiro*-inositol. This property plays an important role in determining its dimensional structure.

The conduritol and inositol dimers were tested for their inhibition properties towards six commercially available glycosidases. The C-2 symmetrical conduritol-F dimer was found to be active against α-mannosidase and β-galactosidase. The conduritol-F dimer was found to be active against α-glucosidase, α-galactosidase and β-galactosidase. The *muco*-inositol dimer was found to be weakly active against α-glucosidase and β-galactosidase.

This project led to valuable insight into the structural and biological properties of the inositol and conduritol oligomers. Higher oligomers (n >2) may be synthesized to reveal the interesting properties such as forming helices which are predicted in the molecular modeling.

As conduritol and inositol oligomers constitute a completely new class of substances, there are almost endless opportunities. The configuration of the inositol can be programmed to form tetramers of specific units to form specific shapes. Molecular modeling have shown that units of L-*chiro, neo-, neo- muco-* inositols may be assemble to form a molecule capable of bonding through three hydroxyls. The presence of the *neo-* inositol units creates a significant turn in the molecule that constructs a cavity that may be utilized for catalyst design. Since these compounds were found to be active on several different glycosidases, they may serve as lead compounds for future studies directed towards enhancing the inhibitory properties of enzymatic processes.

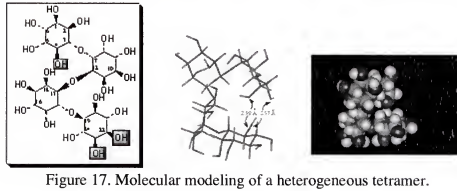


Figure 17. Molecular modeling of a heterogeneous tetramer.

APPENDIX A
EXPERIMENTAL

All non-aqueous reactions were performed using standard techniques for the exclusion of moisture and air. Methylene chloride and dioxane were distilled from calcium hydride, whereas ether and THF were dried over sodium/ benzophenone. Thin-layer chromatography was performed on Silicycle plates and flash chromatography using Natland 200-400 mesh silica gel. Melting points were recorded on Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR or on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini (300 MHz), a Varian VXR (300 MHz), and a Mercury 300 (300 MHz) instrument. All chemical shifts are referenced to TMS or residual undeuterated solvent. Optical rotation was measured on a Perkin Elmer 341 instrument. All combustion analyses were performed by Atlantic Microlab, Norcross GA. Mass spectra were recorded by the analytical division at the University of Florida, Gainesville.

General procedure for the inhibition assays

All measurements were made on a Perkin Elmer 8452A diode array spectrophotometer with a multi-cell attachment.

The following buffers were used for the tests:

Sodium phosphate buffer (25 mM) pH=7.3 for β-galactosidase

Sodium phosphate buffer (25 mM) pH=6.8 for β-glucosidase, α-glucosidase

Sodium phosphate buffer (25 mM) pH=6.0 for α-mannosidase, α-galactosidase

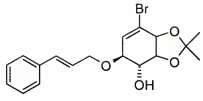
Sodium phosphate buffer (25 mM) pH=5.5 for β-mannosidase

The inhibitor concentration was kept around 1 mg/mL. All tests were run at 37°C, except for the α-mannosidase test, which was performed at 25°C. The substrate concentration was 5 mM except for the α- and β-mannosidase assay were it was 2.5 mM. The enzyme concentration was adjusted to produce a slope of about 0.02-0.025 except for the β-mannosidase assay, were it was adjusted to give a slope of 0.005-0.01. The final volume (adjusted with the corresponding buffer) was 1000 μL in all cases.

To a solution of varying amounts of inhibitor (usually 0-400 mL) in the corresponding buffer solution was added 100 μL of the enzyme solution, except for one vial that was run as a blank to correct for the autohydrolysis of the substrate. All samples were pre-incubated at the corresponding temperature for 5 minutes, after which the reaction was started by addition of the substrate (400 μL). The absorption was then recorded over a period of 10 minutes by continually scanning all samples. The slopes obtained for the individual samples were then plotted against the inhibitor concentration to obtain the usual inhibition curves.

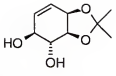
3-Bromo-5,5-dimethyl-1a,3a,6a,6b-te trahydro-1,4,6-trioxa-cyclopropa[e] indene (**390**)

To a solution of acetonide **196** (5.00 g, 21.64 mmol) in CH_2Cl_2 (50 ml) was added *m*CPBA (5.58g, 32.47 mmol) in one portion. The reaction mixture was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure. The crude product was purified by recyrstallization from hexanes to afford (3.85 g, 72%) of white crystals. Spectra data of this compound matched the literature reported data [110]



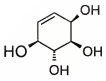
7-Bromo-2,2-dimethyl-5-(3-phenyl-allyloxy)-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-ol (**530**)

The vinyl epoxide **390** (0.814 mg; 3.30 mmol) was dissolved in dry CH_2Cl_2 in a flame-dried flask. Cinnamyl alcohol (2.21g, 16.48 mmol) was added and stirred at -20 ^{0}C. $BF_3{\cdot}OEt_2$ (catalytic) was added. The reaction was stirred for overnight at room temperature. The reaction was quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2. The solvent was removed in vacuo and the residue purified by flash chromatography (100% CH_2Cl_2) to yield 655 mg white solid. m.p. 97-100 ^{0}C, R_f = 0.32 (100% CH_2Cl_2); $[\alpha]_D^{28}$+27.67 ; IR (film on NaCl) 3453, 3058, 1646, 11380,1217, 1072, cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5H), 6.64 (d, J = 16.2 Hz, 1H), 6.28 (m, 2H), 4.32 (m, 2H), 4.12 (m, 1H),, 3.88 (d, J =8.4 Hz, 2H), 3.72 (t, J = 8.7 Hz, 1H), 2.71 (bs, 1H), 1.56 (s, 3H), 1.42 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.71, 133.84, 133.42, 129.04, 128.41, 127.01, 125.42, 119.06, 111.48, 78.50, 77.60, 73.26, 71.24, 28.58, 26.39; LRMS(EI) 190,172,133, 91: HRMS (FAB) calcd. for ($C_{18}H_{21}BrO_4$+H) 381.27; Found:382.0461 (M+1); Anal. Calcd. C 56.71%, H 5.55%,. Found:C 56.36%, H 5.46%.



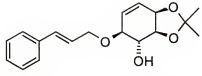
2,2-Dimethyl-3a,4,5,7a-tetrahydro-b
enzo[1,3]dioxole-4,5-diol (**305**)

The electrolysis cell consisted of a 150mL beaker, bromide **530** (283mg, 0.743mmol), a mercury pool electrode, a simple Ag/Ag^+ reference electrode, platinum foil in a divided cell as the auxiliary electrode. An EG & G Princeton Applied Research Potentiostat-Galvanostat Model 263A maintained the desired voltage. A 0.1 M solution of the charge carrier (Et_4NBr) in acetonitrile was added to the cell and allowed to equilibrate with the divided cell. Phenol (2.0 equivalents) was added. Excess oxygen was expelled from the electrochemical cell by passing an argon stream through the reaction mixture for 10 minutes. The reaction was performed at -2.65 V until TLC analysis indicated disappearance of the starting material. The reaction mixture was diluted with ethyl ether and the charge carrier precipated out of solution. The solid was filtered and the filtrate was concentrated. The residue was purified by chromatography (100% EtOAc) to yield 0.101 g (73%) of white solid. m.p. 136-138 °C (lit. value 136-137 °C).[213]



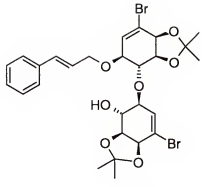
Conduritol F (**15**)

Acetonide **305** (42mg, 0.226 mmol) was dissolved in a 4:1:1 mixture of tetrahydrofuran: triflouroacetic acid and H_20 (2 mL). The mixture was allowed to stand at room temperature for 20 hours after which a white precipitate had formed. The crystals were filtered and washed with methylene chloride to afford **15** in 94% yield (31 mg) as white crystals. Spectra data of this compound matched the literature reported data. m.p. 125-127 °C (lit. value 128-129 °C).[214]



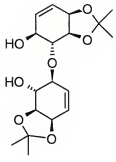
2,2-Dimethyl-5-(3-phenyl-allyloxy)-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-ol (**531**)

The electrolysis cell consisted of a 150mL beaker, alcohol **530** (0.264 mg, 0.693 mmol), a carbon electrode, a simple Ag/Ag^+ reference electrode,and platinum foil in a divided cell as the auxiliary electrode. An EG & G Princeton Applied Research Potentiostat-Galvanostat Model 263A maintained the desired voltage. A 0.1 M solution of the charge carrier (Et_4NBr) in acetonitrile was added to the cell and allowed to equilibrate with the divided cell. Phenol (2.0 equivalents) was added. Excess oxygen was expelled from the electrochemical cell by passing an argon stream through the reaction mixture for 10 minutes. Alcohol **530** was dissolved in acetonitrile and added to the main compartment. The reaction was performed at -2.65 V until TLC analysis indicated disappearance of the starting material. The reaction mixture was diluted with ethyl ether and the charge carrier precipated out of solution. The solid was filtered and the filtrate was concentrated. The residue was purified by chromatography (9:1 CH_2Cl_2) to yield 137 mg (66%) of viscous oil. $[\alpha]_D^{27}$ = -17.7 (c=1.05, $CHCl_3$); R_f = 0.35 (7:3 Hexanes: EtOAc); IR (film on NaCl) 3461, 3058, 1382, 1072, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 5H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.30 (tt, J = 15.9, 6.0 Hz, 1H), 5.92 (m, 2H), 4.34 (m, 2H), 4.12 (m, 2H), 3.90 (t, *J* =7.5 Hz, 2H), 3.69 (t, *J* = 9.3 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.63, 133.13, 131.91, 128.78, 128.04, 126.73, 125.76, 124.08, 110.73, 77.99, 73.79, 72.58, 70.81, 28.33, 25.93; HRMS (FAB) calcd. For ($C_{18}H_{22}rO_4$+H) 303.3816; Found 303.2512; Anal. Calcd. for C 71.50 %, H 7.33%,. Found: C 68.81%, H 7.36.



7-Bromo-5-[7-bromo-2,2-dimethyl-5-(3-phenyl-allyloxy)-3a,4,5,7a-tetrah ydro-benzo[1,3]dioxol-4-yloxy]-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo [1,3]dioxol-4-ol (**532**)

The vinyl epoxide **390** (0.405 g; 1.64 mmol) was dissolved in dry CH_2Cl_2 in a flame-dried flask. Alcohol **530** (0.625 g, 1.64mmol) was added and stirred at -20 ^{0}C. 10% BF_3OEt_2 was added. The reaction was stirred for 1 h at -20 ^{0}C. The reaction was quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2. The solvent was removed in vacuo and the residue purified by flash chromatography (100% CH_2Cl_2) to yield 0.566 mg of white solid m.p 171-172 ^{0}C, $[\alpha]_D^{28}$ +42.45(c=1.05, $CHCl_3$); R_f= 0.29 (100% CH_2Cl_2); IR (film on NaCl) 3461, 3058, 1382, 1072, cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.31 (m, 3H), 4.68 (dd, *J* = 6.6, 24 Hz, 2H), 4.39 (m, 2H), 4.19 (m, 2H), 3.91 (t, *J* =7.5 Hz, 2H), 3.67 (t, *J* = 8.7 Hz, 1H), 3.54 (, *J* = 8.7 Hz, 1H), 1.57 (m, *3*H), 1.41 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.26, 135.20, 134.27, 133.71, 133.15, 132.85, 128.83, 128.30, 126.87, 124.40, 118.23, 118.04, 84.43, 84.24, 78.63, 77.21, 74.71, 73.00, 70.15, 28.30, 27.83, 25.98, 25.76; HRMS (FAB) calcd. for ($C_{27}H_{32}Br_2O_7$-CH_3) 613.0258; Found: 613.3359; Anal. Calcd. for C 51.61%, H 5.13%, Found;C 51.70%, H 5.26%.

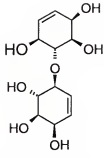


5-(5-Hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yloxy)-2,2,7-trimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-ol(**533**)

The electrolysis cell consisted of a 150 mL beaker, bromide **532** (180 mg, 0.287 mmol), a carbon electrode, a simple Ag/Ag^+ reference electrode, and platinum foil in a divided cell as the auxiliary electrode. An EG & G Princeton Applied Research Potentiostat-Galvanostat Model 263A maintained the desired voltage. A 0.1 M solution of the charge carrier (Et_4NBr) in acetonitrile was added to the cell and allowed to equilibrate with the divided cell. Phenol (2.0 equivalents) was added. Excess oxygen was expelled from the electrochemical cell by passing an argon stream through the reaction mixture for 10 minutes. The starting material was dissolved in acetonitrile and added to the main compartment. The reaction was performed at -3.02 V until TLC analysis indicated disappearance of the starting material. The reaction mixture was diluted with ethyl ether and the charge carrier precipated out of solution. The solid was filtered and the filtrate was concentrated. The residue was purified by chromatography (7:3 Hexane:Ethyl Acetate) to yield 40 mg (40%) of vicous oil.

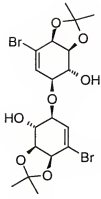
m.p. 1-198 ^0C $[\alpha]_D^{28}$ -20.5(c=1.00, $CHCl_3$); R_f = 0.29 (100% CH_2Cl_2); IR (film on NaCl) 3461, 3058, 2875, 1382, 1072, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), 6.07 (d, J = 1.2 Hz, 1H), 5.85 (m, 3H), 4.64 (m, 2H), 4.36 (s, 1H), 4.23 (dd, J =9.0, 6.9 Hz 1H), 4.12 (m, 2H), 3.69 (t, J =9.0 Hz, 1H), 3.50 (t, J = 8.7 Hz, 1H), 1.51 (m, 6H), 1.38 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.41, 133.62, 123.74, 123.34, 110.91, 110.65, 84.84, 82.00, 77.51,

74.53, 73.06, 72.46, 70.65,60.58, 28.29 27.85, 25.85, 25.61; HRMS (FAB) calcd. For ($C_{18}H_{26}O_7$ + H) 355.4117; Found:355.1765



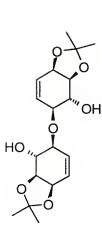
6-(2,5,6-trihydroxy-cycloh ex-3-enyloxy)-cyclohex-4-ene-1,2,3-triol(**534**)

Dimer **533** (40 mg, 0.113 mmol) was dissolved in a 4:1:1 mixture of tetrahydrofuran: triflouroacetic acid and H_20 (2 mL). The mixture was allowed to stand at room temperature for 20 hours after which a white precipitate had formed. The crystals were filtered and washed with methylene chloride to yield **534** (29 mg) as white crystals. m.p. 220-222 ^{0}C (decomp); $[\alpha]_D^{28}$ -9.8 (C=0.90, MeOH); IR (KBr) 3432, 3041, 1045, cm^{-1}; ^{1}H NMR (D_2O, 300 MHz), 5.87 (d, J = 11.4 Hz, 1H), 5.72(m, 3H), 4.14 (m, 2H), 4.02 (m, 2H), 3.68 (t, J =10.8 Hz 1H), 3.60 (d, J =3.9 Hz , 2H), 3.49 (dd, J =3.9, 4.2 Hz, 1H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.76, 130.95, 127.30, 126.75, 83.61, 83.23, 72.34, 71.95, 71.37, 70.72, 67.00, 66.72; HRMS (FAB) calcd. for ($C_{12}H_{18}O_7$ + H) 275.2811, Found:275.2315.



7-Bromo-5-(7-bromo-4-hydro-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-5-yloxy)-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-ol(**535**)

A mixture of epoxide **390** that had been left to hydrolyzed in a container open to the atmosphere was purified by column chromatography(7:3 Hexane:Ethyl Acetate). m.p. 204-205 ^{0}C, R_f= 0.37 (1:1 Hex/EtOAc); IR (film on NaCl) 3249,2987, 1383, 1246, 1216, 1065 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 6.41 (s, 2H), 4.70 (d, *J* = 6.6 Hz, 2H), 4.12 (dd, *J*=9.3, 6.3 Hz, 2H), 3.95 (dd, J=8.4, 1.2 Hz, 2H), 3.50 (t, J=8.7 Hz, 2H), 1.48 (s, 6H), 1.37 (s, 6H); ^{13}C NMR (CD_3OD, 75 MHz) δ 135.87, 119.12, 111.61, 81.73, 79.30, 78.68, 73.62, 28.49, 26.22; LRMS(EI) 190,172,133, 91: HRMS (EI) calcd. for ($C_{18}H_{24}Br_2O_7 + H^+$) calcd. for 512.1958; Found:512.9857 Anal. Calcd. C 42.21%, H 4.72%, Found: C 42.43%, H 4.76%.

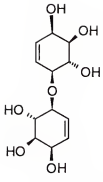


5-(4-hydro-2,2-dimethyl-3a,4,5,7a -tetrahydro-benzo[1,3]dioxol-5-ylox y)-2,2-dimethyl-3a,4,5,7a-tetrahydr o-benzo[1,3]dioxol-4-ol(**536**)

The electrolysis cell consisted of a 150mL beaker, dimer **535** (208 mg, 0.407 mmol), a carbon electrode, a simple Ag/Ag^+ reference electrode, and platinum foil in a divided cell as the auxiliary electrode. An EG & G Princeton Applied Research Potentiostat-Galvanostat Model 263A maintained the desired voltage. A 0.1 M solution of the charge carrier (Et_4NBr) in acetonitrile was added to the cell and allowed to equilibrate with the divided cell. Phenol (2.0 equivalents) was added. Excess oxygen was expelled from the electrochemical cell by passing an argon stream through the reaction mixture for 10 minutes. The starting material was dissolved in acetonitrile and added to the main compartment. The reaction was performed at -2.40 V until TLC analysis indicated disappearance of the starting material. The reaction mixture was diluted with ethyl ether and the charge carrier precipated out of solution. The solid was filtered and the filtrate was concentrated. The residue was purified by chromatography (7:3 Hexane:Ethyl Acetate).to yield 96mg (73%) of white solid.

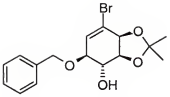
m.p. 196-198 ^{0}C; R_f = 0.31 (1:1 Hex/EtOAc); IR (film on NaCl) 3503, 2987, 1381, 1372, 1216, 1056 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.13 (m, 4H), 4.82 (dd, *J* = 2.7, 6.3 Hz, 2H), 4.29 (dd, *J*=9.3, 6.6, Hz, 2H), 4.24 (dd, J= 9.0, 1.5, Hz, 2H), 3.87 (t, J=9.0 Hz, 2H), 3.61 (s, 2H), 1.72 (s, 6H), 1.59 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.76, 124.37,

110.62, 77.51, 76.50, 72.70, 72.31 28.13, 25.74; LRMS(EI) 352, 335, 254, 177, 111; ; HRMS (FAB) calcd. for ($C_{18}H_{26}O_7$ + H) calcd. for 355.4037; Found:355.1753 Anal. Calcd. C 61.00%, H 7.39%. Found: C 60.87%, H 7.39%.



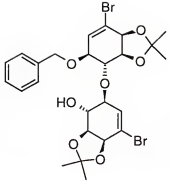
6-(4,5,6-trihydroxy-cycloh ex-2-enyloxy)-cyclohex-4-ene-1,2,3-triol (**537**)

Dimer **536** (96 mg, 0.271 mmol) was dissolved in a 4:1:1 mixture of tetrahydrofuran: triflouroacetic acid and H_20 (2 mL). The mixture was allowed to stand at room temperature for 20 hours after which a white precipitate had formed. The crystals were filtered and washed with methylene chloride to yield **537** (74 mg) as white crystals. m.p. 144-147 °C, IR (film on NaCl) cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ) δ 5.97 (dd, J= 2.1,1.8 Hz , 2H), 5.79 (m, 2H), 4.15 (t, *J*=4.5, Hz, 2H), 4.00 (d, J= 7.5, Hz, 2H), 3.71 (m, 2H), 3.43 (dd, J= 4.2, 3.9 Hz, 2H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.76, 128.17, 82.49, 72.88, 72.62, 68.85, 68.03,; LRMS(EI) 352, 335, 254, 177, 111;HRMS (FAB) calcd. for ($C_{12}H_{18}O_7$ + H) 275.281, Found:275.1124



3-Bromo-5,5-dimethyl-1a,3a,6a,6b-te trahydro-1,4,6-trioxa-cyclopropa[e] indene (**352**)

To a flame dried flask was added epoxide **390** (3.00 g, 12.15 mmol) dissolved in anhydrous CH_2Cl_2. The solution was cooled with an ice bath to 0°C. To the mixture was added BnOH (6.28 mL, 60.73 mmol) followed by BF_3-OEt_2 (0.154 mL, 1.215 mmol) and the solution was warmed to room temperature for 30 minutes. The solvent was removed in vacuo and the mixture separated via flash chromatography (Hexanes:Ethyl acetate 5:1). The product was obtained in 3.23 g (75%) of a white solid. Spectra data of this compound matched the literature reported data.[186]



5-(5-Benzyloxy-7-bromo-2,2-dimethyl
-3a,4,5,7a-tetrahydro-benzo[1,3]dio
xol-4-yloxy)-7-bromo-2,2-dimethyl-3
a,4,5,7a-tetrahydro-benzo[1,3]dioxo
l-4-ol (**470**)

The alcohol **352** (1.15 mg; 3.24 mmol) was dissolved in dry CH_2Cl_2 in a flame-dried flask. Vinyl epoxide **390** (0.761 g, 3.08 mmol) was added and stirred at -20 ^{0}C. 10% $BF_3{\cdot}OEt_2$ was added. The reaction was stirred for 1.5 h at -20 ^{0}C. The reaction was quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2. The solvent was removed in vacuo and the residue purified by flash chromatography (100% CH_2Cl_2) to yield 1.57 mg of white solid. m.p. 188-189 ^{o}C (lit. value 188-189 ^{o}C).[186]

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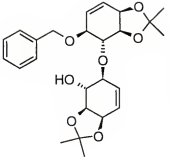
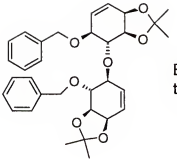


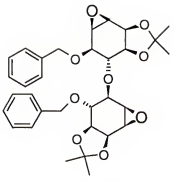
5-(5-Benzyloxy-2,2-dimethyl-3a,4,5,
7a-tetrahydro-benzo[1,3]dioxol-4-yl
oxy)-2,2-dimethyl-3a,4,5,7a-tetrahy
dro-benzo[1,3]dioxol-4-ol (**539**)

The electrolysis cell consisted of a 150 mL beaker, bromide **470** (1.09 mg, 1.81 mmol), a mercury pool electrode, a simple Ag/Ag^+ reference electrode, and platinum foil in a divided cell as the auxiliary electrode. An EG & G Princeton Applied Research Potentiostat-Galvanostat Model 263A maintained the desired voltage. A 0.1 M solution of the charge carrier (Et_4NBr) in acetonitrile was added to the cell and allowed to equilibrate with the divided cell. Phenol (2.0 equivalents) was added. Excess oxygen was expelled from the electrochemical cell by passing an argon stream through the reaction mixture for 10 minutes. The alcohol **470** was dissolved in acetonitrile and added to the main compartment. The reaction was performed at -2.65 V until TLC analysis indicated disappearance of the starting material. The reaction mixture was diluted with ethyl ether and the charge carrier precipated out of solution. The solid was filtered and the filtrate was concentrated. The residue was purified by chromatography (9:1 CH_2Cl_2) to yield 0.616g (77%) of white solid. Spectra data of this compound matched the literature reported data. m.p. 69-71 °C (lit. value 71-74 °C). [186]



Bis-(5-Benzyloxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-ol (**544**)

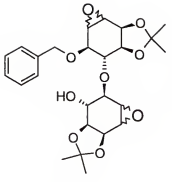
To a flame dried flask was added alcohol **539** (140 mg, 0.316 mmol) dissolved in anhydrous THF. To the mixture was added NaH (11.3 mg, 0.4.74 mmol). Benzyl bromide (75 μL, 0.632 mmol) was added and the solution was sitr at room temperature for 18 hours. The reaction was quenched with H_2O and extracted with CH_2Cl_2. The solvent was removed in vacuo and the residue purified by flash chromatography (95:1 hexanes:ethyl acetate) to yield 135 mg of viscous oil in 80% yield. $[\alpha]_D^{27}$ = 69.3 (c=1.1, $CHCl_3$); R_f = 0.42 (8:2 Hex/EtOAc); IR (film on NaCl) cm^{-1}; 3502, 3032, 2986, 2933, 1497, 1380, 1059, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46 (m, 2H), 7.30 (m, 8H), 6.10 (d, J= 10.2 Hz, 1H) 5.82 (m, 3H), 4.94 (q, J= 11.7 Hz , 2H), 4.69 (q, J= 12 Hz, 2H), 4.56 (m, 3H), 4.24 (m, 2H), 3.87 (dd, J= 1.8, 1.5, Hz, 1H), 2.72 (t, J= 7.8 Hz, 1H), 3.56 (t, J= 8.1 Hz, 1H), 1.47 (s, 3H), 1.44 (s,3H), 1.38 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.35, 138.23, 138.21, 132.38, 131.68, 131.61, 128.29, 127.98, 127.89, 127.86, 127.68, 127.65, 127.59, 127.07, 124.24, 122.87, 110.00, 109.92, 80.45, 79.75, 78.32, 78.29, 77.64, 76.69, 73.94, 72.88, 72.73, 72.47, 26.10, 27.93, 25.91, 25.58; LRMS(EI) 469, 259, 91 Anal. Calcd. C 71.89%, H 7.16%, Found: C 71.03%, H 7.17%.



bis-(2 -Benzyloxy-5,5-dimethyl-hexahydro-1,4,6-trioxa-cyclopropa[e]inden-3-ol (**545**)

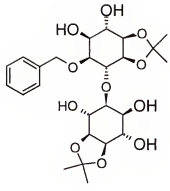
To a flask was added alcohol **544** (103 mg, 0.0.232 mmol) dissolved in a mixture of acetone:H_2O (5:1) at 0 °C. DBH was added and after 20 minutes was allowed to warm to room temperature. The solution was sitr at room temperature for 3 hours. The reaction was quenched with 10% $NaSO_3$ and extracted with CH_2Cl_2. The solvent was removed in vacuo. The bromohydrin was solved in DME and cooled to 0 °C. NaOH (10%) was added dropwise. The reaction was allowed to warm to room temperature and stir for 2 hours. The solvent was removed in vacuo and residue was extracted with CH_2Cl_2. The residue was purified by flash chromatography (9:1 hexanes:ethyl acetate) to yield 33 mg of clear viscous oil in 30% yield.

$[\alpha]_D^{28}$ = -71.5 (c=1.0, $CHCl_3$); R_f = 0.41 (8:2 Hex/EtOAc); IR (film on NaCl) cm^{-1}; 3502, 3032, 2986, 2933, 1380, 1060, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 10H), 4.79 (m, , 3H), 4.69 (m, 1H), 4.52 (t, J=5.7 Hz, 2H), 4.05 (m, 2H), 3.98 (dd, J= 7.8, 8.1 Hz, 1H), 3.72 (t, J= 7.8 Hz, 1H), 3.51 (dd, J= 8.4, 8.1 Hz, 1H), 3.43(m, 1H) 3.31 (dd, J= 3.3, 3.6) 1.54 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 1.35 (3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.77, 137.44, 128.49, 128.10, 127.99 127.93, 127.83, 127.34, 78.80, 78.52, 77.62, 76.36, 75.97, 75.66, 73.98, 73.15, 72.28, 72.12, 55.64, 55.28, 52.51, 52.37, 27.92, 25.84, 25.90, 25.75; LRMS(EI) 552, 475,439,108.



2-(2-Benzyloxy-5,5-dimethyl-hexahyd
ro-1,4,6-trioxa-cyclopropa[e]inden-
3-yloxy)-5,5-dimethyl-hexahydro-1,4
,6-trioxa-cyclopropa[e]inden-3-ol(**542**)

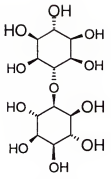
Diene **539**(110 mg, 0.248 mmol) was stirred in acetonitrile (10 ml). Na_2EDTA (4mL) was added. The reaction mixture was cooled to O °C. Trifluoroacetone was added via a cooled syringe. To this mixture, $NaHCO_3$ (1.30g, 64.4 mmol) and Oxone (3.07g, 5.0 mmol) was added and stirred for 45 mins at O °C. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. . The solvent was removed in vacuo and the residue purified by flash chromatography (8:2 hexanes:ethyl acetate) to yield 48 mg of mixture of epoxides. IR (film on NaCl) 3449.21, 2989, 1701, 1382, 1073 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 7.47 (m, 10H), 4.61 (m, 4H), 4.13-3.30 (m, 24H),1.53 (m, 12H), 1.38(m, 12H); ^{13}C NMR (D_2O, 75 MHz) δ 133.53, 130.07, 128.59, 128.51, 128.16, 110.55, 110.19, 110.05, 109.87, 84.28, 82.52, 81.89, 79.06, 78.54, 78.07, 77.73, 76.65, 75, 24, 73.67, 73.67, 73.02, 72.89, 72.57, 72.23, 72.01, 68.49, 57.15, 57.03, 56.62, 55.89, 52.63, 52.61, 52.37, 52.33, 52.08, 27.91, 27.75, 27.57, 26.98, 25.56, 24.70. HRMS calcd. For ($C_{25}H_{32}O_7$-H] 475.5204, Found: 475.1779.



6-(5-Benzyloxy-6,7-dihydroxy-2,2-di methyl-hexahydro-benzo[1,3]dioxol-4 -yloxy)-2,2-dimethyl-hexahydro-benz o[1,3]dioxole-4,5,7-triol (**541**)

To a flask was added diepoxide **542** (79 mg, 0.166 mmol) and dissolved in H_2O. Amberlyst resin (strongly basic)(79 mg) was added and the reaction was adjusted to a pH 10 by addition of 10% KOH. The reaction mixture was stirred at reflux for 6 days. The product was recovered by continous aqueous extraction to afford 51 mg of white solid in 61% yield.

m.p. 209-212 ^{0}C (decomp.) $[\alpha]_D^{26}$ = -21.2 (c=1.2, H_2O); IR (KBr) cm^{-1}; 3502, 3039, 2984, 2933, 1497, 1061, ^{1}H NMR (D_2O, 300 MHz) δ 7.33 (m, 5H), 4.45-3.15 (m, , 14H),1.35 (m, 6H), 1.21(m, 6H); ^{13}C NMR (D_2O, 75 MHz) δ 139.98, 129.20, 120.96, 128.54, 110.10, 110.07, 80.94, 80.53, 80.40, 73.40, 72.51, 71.21, 69.48, 49.71, 49.42, 49.14, 48.85, 48.57, 32.77, 28.54, 26.36, 23.74; LRMS(FAB) 497, 405, 93.



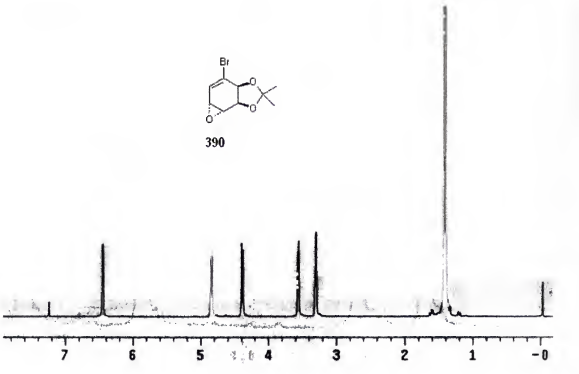
muco-Inositiol dimer
(**541**)

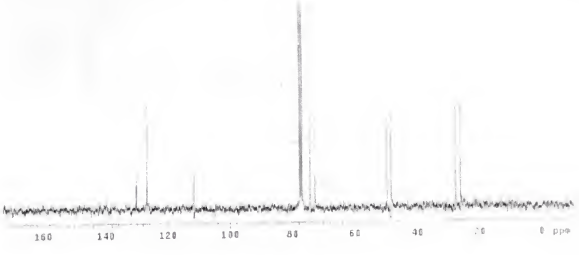
To a flask was added cyclitol **549** (51 mg, 0.099 mmol) and dissolved in a mixture of MeOH (2 ml) and 100 μL of conc. HCl. Pd/C (51 mg) was added. The reaction was stirred for 18 hours at room temperature under a hydrogen atmosphere. The Pd/C was filtered and the solvent was removed in vacuo to yield a white solid.

m.p. >250 ^{0}C; $[\alpha]_{D}^{33}$ = -28.2 (c=1.1, H_2O); IR (KBr) 3322, 2884, 1396, 1238, 901, 866 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 3.98-3.10 (m, 12H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 77.45, 73.43, 72.67, 72.54, 71.72, 71.59, 71.30, 71.00, 70.73, 70.17, 69.59, 69.10; HRMS calcd. for 342.1160, Found:342.1142.

APPENDIX A
SELECTED SPECTRA

390





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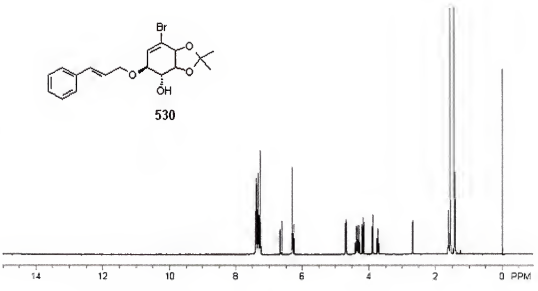

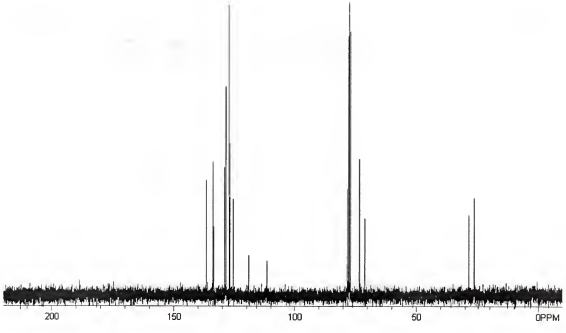

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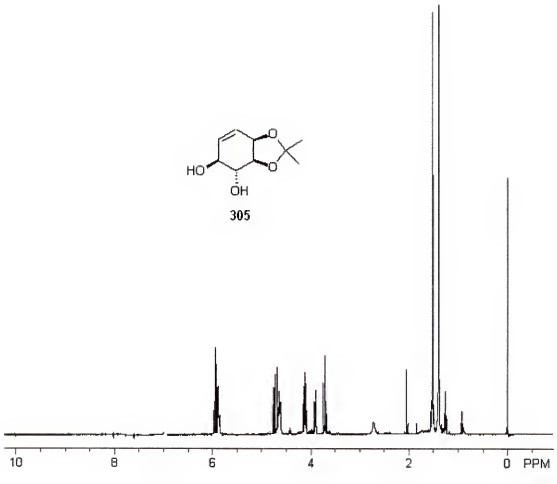

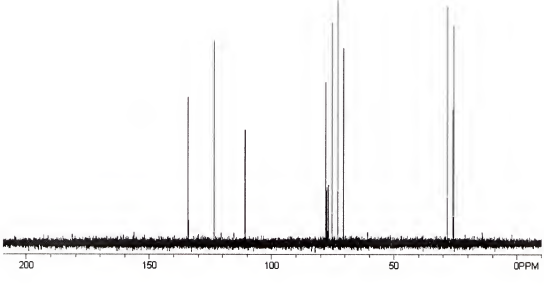

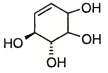

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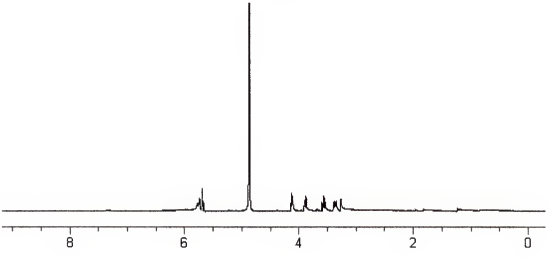

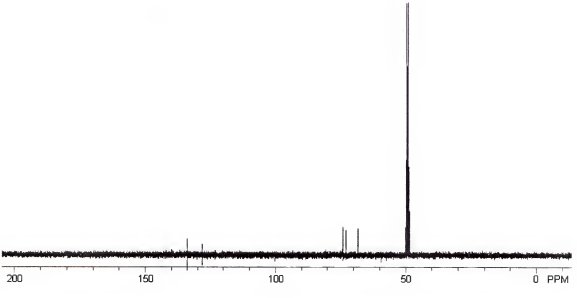

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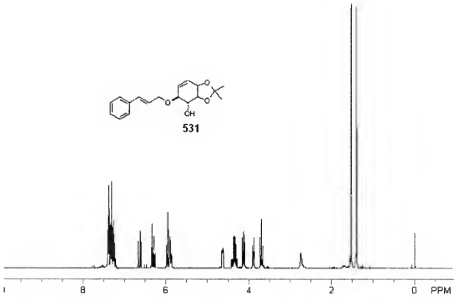

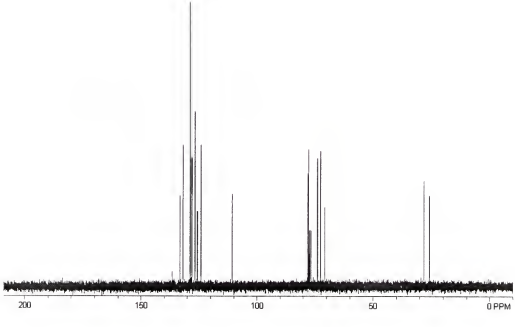

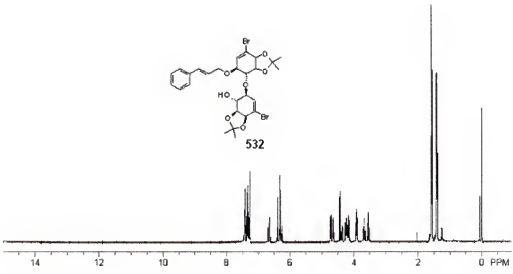

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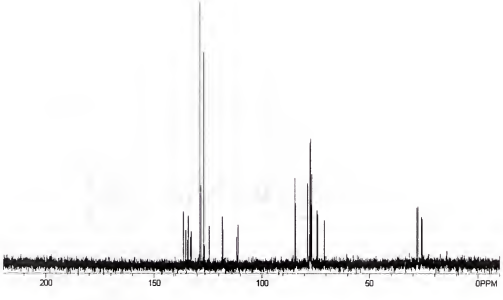

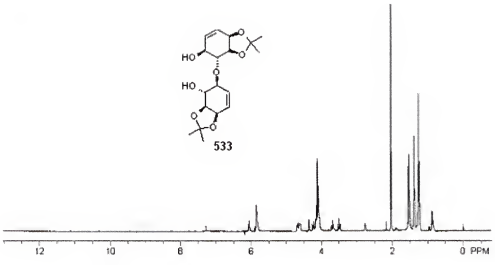
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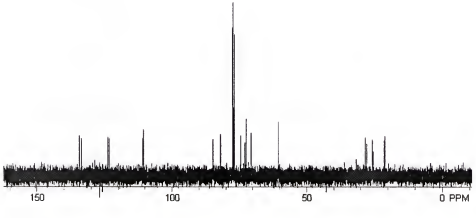
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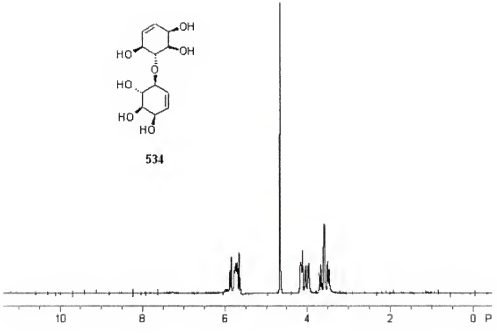

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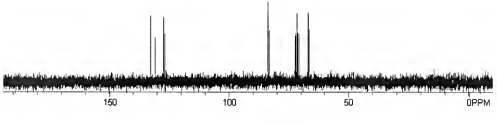

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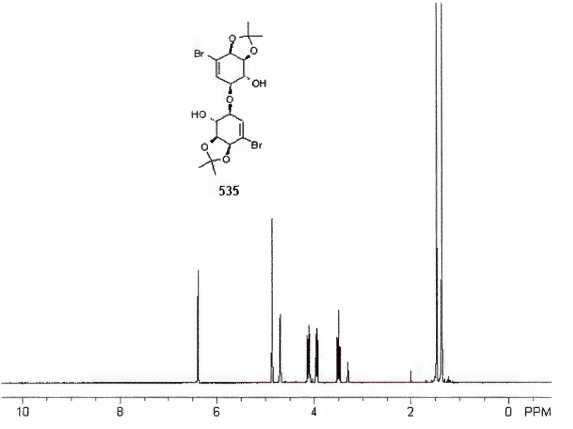

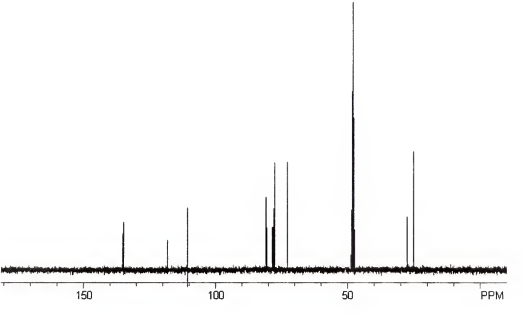

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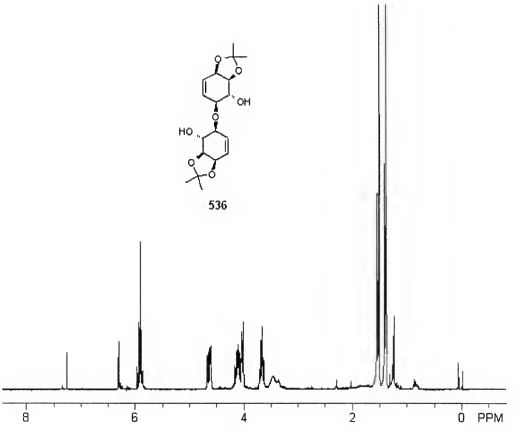

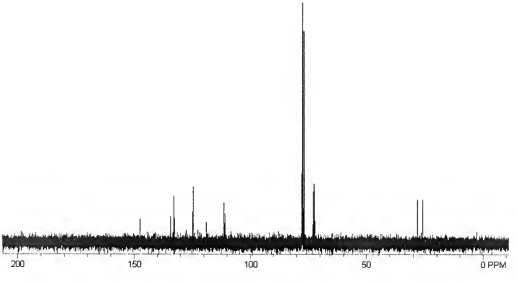

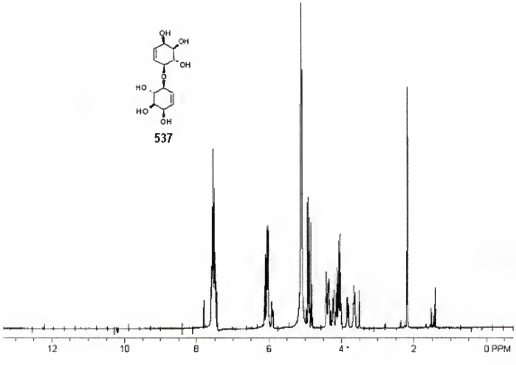

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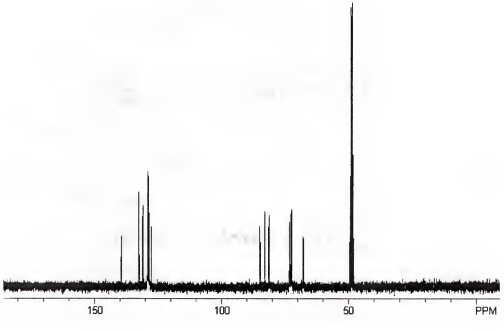

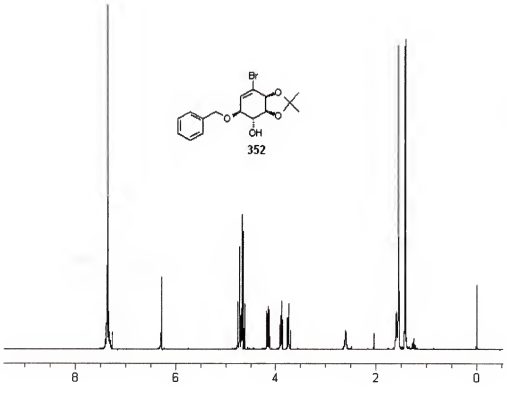

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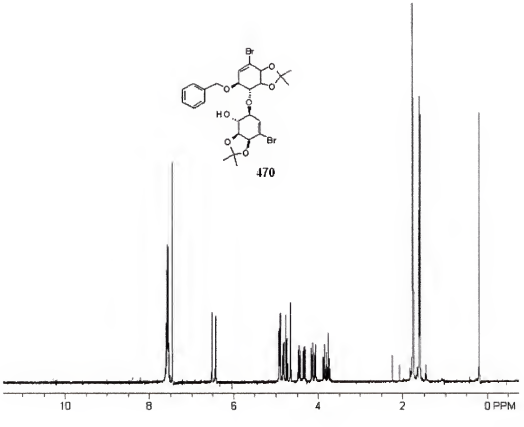

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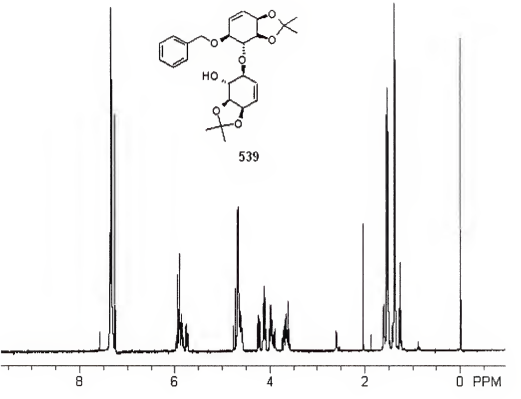

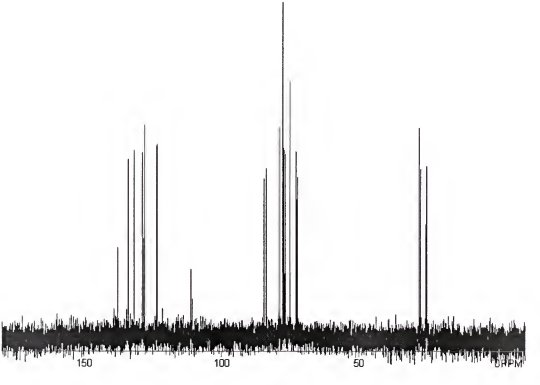

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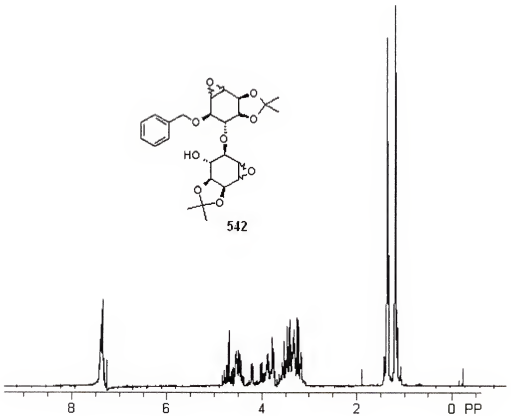

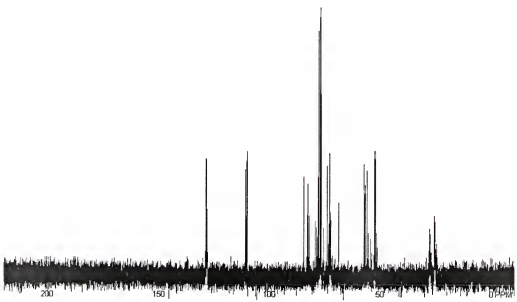

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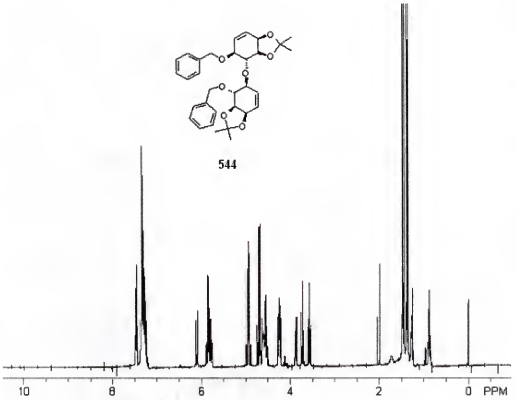

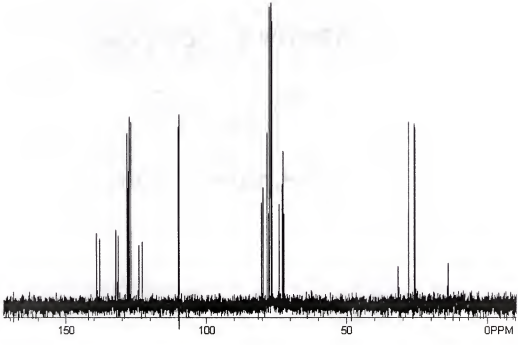

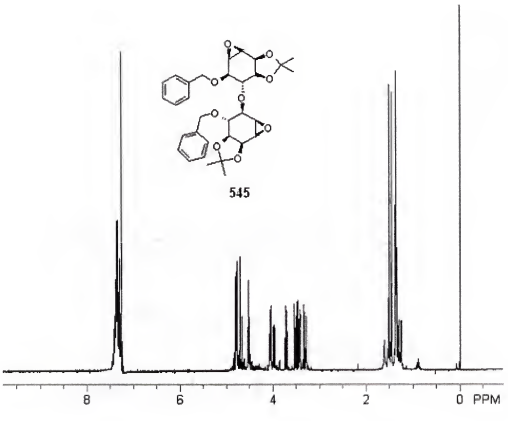

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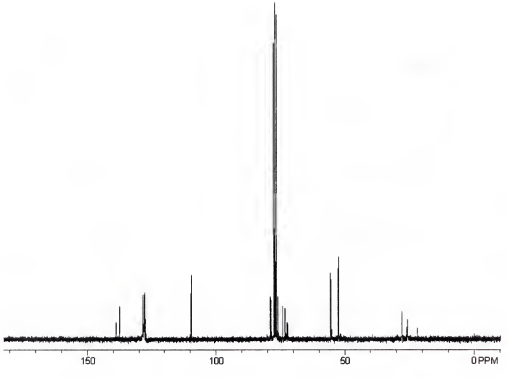

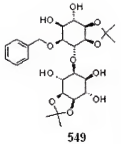

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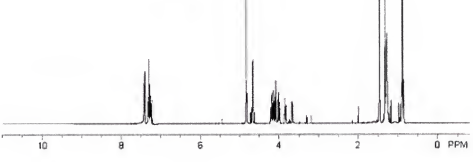

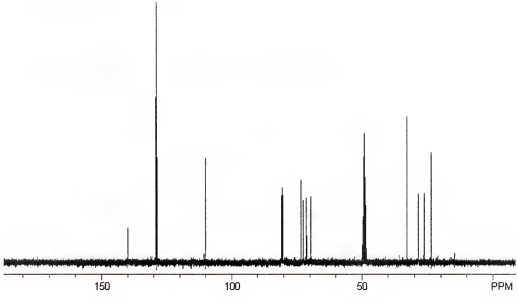

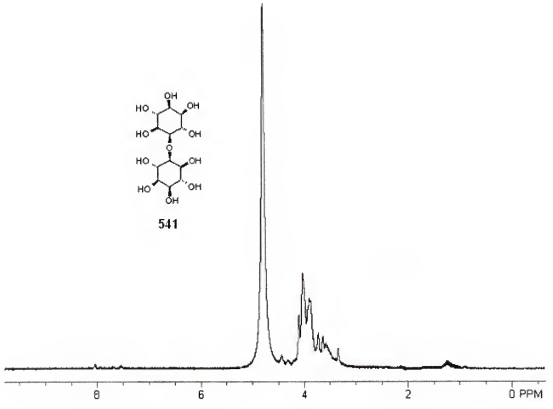

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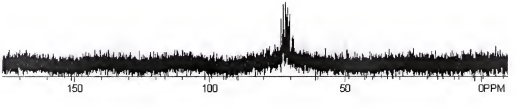

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BIOGRAPHICAL SKETCH

Stanley Freeman was born May 16, 1972, in Lithonia, Georgia. He received his high school diploma from Lithonia High School in June 1990. He attended Hampton University, in Hampton, Virginia, where he was awarded a United States Department of Energy's Environmental Career Opportunities for Minorities (EMCOM) scholarship. He earned his bachelor's degree in chemistry on May 14, 1995. The author enrolled in graduate school at the University of Florida in August 1995 where he received a McKnight Doctoral Fellowship from the Florida Educational Fund. Under the supervision of Professor Tomas Hudlicky, the author earned his Master's degree in the area of organic synthesis. In August 1997, Stanley accepted a position with Merck Research Laboratories in Rahway, NJ. At Merck, the author was awarded a Merck Research Laboratories Doctoral Fellowship were he return to the University of Florida to continue working with Professor Hudlicky. His major area of focus has been the synthesis of cyclitol oligomers utilizing a combination of enzymatic, electrochemical, and basic synthetic organic chemistry methods.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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